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Simulation and Analysis of Policies for the Allocation of Liver Transplants

by

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**A thesis submitted in partial fulfilment of the requirements for
the degree of
Doctor of Philosophy in Industrial and Business Studies**

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Declaration of Authorship

I, Suchi Patel, declare that this thesis entitled

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and the work present in it are my own. I confirm that:

- This work was done wholly or mainly while in candidature for this research degree;
- Where any part of this thesis has previously been submitted for a degrees or any other qualification at this University or any other institution, this has been clearly stated;
- Where I have consulted the published work of others, this is always clearly attributed;
- Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
- I have acknowledged all main sources of help;
- Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself; and
- During the preparation of this thesis, several papers were presented and published as listed below. The remaining parts of the thesis have not yet been published.

The EURO Working Group of OR applied to Health Services, Prague, 27 July-1 August 2003. *Presentation and paper for proceedings: 'Liver Transplant Models - A Review and More...'*

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Date:

Abstract

Liver transplantation is a vital medical procedure as it helps to prolong the lives and improve the quality of life for a number of people suffering from end stage liver diseases. Unfortunately though, there is a limit to the number of people that may benefit from the operation due to a shortage in the number of livers that are donated. This shortage, conflicting viewpoints, and a changing mix of patients requiring liver transplantation means that it is important to make sure that the livers which are donated are used to their greatest potential (utility) and allocated in a way which is seen as fair (equity). This thesis considers various transplant assessment rule, allocation rule, demand and supply scenarios, to aid in the understanding of the dynamics of the liver transplantation process, and in identifying situations in which equity and utility improve.

Survival and Competing Risks Models identify key patient, donor and transplant attributes which influence a patients' progression through the system.

A Discrete Event Simulation model is developed to assess the equity and utility outcomes for how a particular scenario allocates liver transplants to patients. Parametric distributions generated from relevant Survival and Competing Risks models are used to predict the events a patient will experience and to estimate the times at which they will experience the events.

Some of the key insights gained into decision making within the UK Liver Transplantation System, are: (1) the need to implement simple rules and rules which change over time, to obtain the best equity and utility output measures as supply, demand and patient mix change; and (2) it is easier to improve the overall utility in the system than the equity, due to the implications of prioritisation.

Abbreviations

<i>ABO</i>	A, B, O, or AB blood groups
<i>AFT</i>	Accelerated Failure Time
<i>ALD</i>	Acute Liver Disease
<i>BLU</i>	Birmingham Liver Unit
<i>BMI</i>	Body Mass Index
<i>CLD</i>	Chronic Liver Disease
<i>CR</i>	Competing Risks
<i>DES</i>	Discrete Event Simulation
<i>DGF</i>	Death or Graft Failure
<i>DoH</i>	Department of Health
<i>DR</i>	Death or Removal
<i>ESLD</i>	End Stage Liver Disease
<i>FCFS</i>	First-Come first-served
<i>HCV</i>	Hepatitis C Virus
<i>HLA</i>	Human Leukocyte Antigens
<i>HRQoL</i>	Health Related Quality of Life
<i>ICER</i>	Incremental Cost Effectiveness Ratio
<i>ICU</i>	Intensive Care Unit
<i>LY</i>	Life Year
<i>MELD</i>	Model for End stage Liver Disease
<i>NAFLD</i>	Non-Alcoholic Fatty Liver Disease
<i>NASH</i>	Non-Alcoholic Steato-Hepatitis
<i>NHS</i>	National Health Service
<i>ODR</i>	Organ Donor Register
<i>OPTN</i>	Organ Procurement and Transplantation Network
<i>OR</i>	Operational Research
<i>PBC</i>	Primary Biliary Cirrhosis
<i>PH</i>	Proportional Hazard
<i>PSC</i>	Primary Sclerosing Cholangitis
<i>QALY</i>	Quality Adjusted Life Year
<i>QoL</i>	Quality of Life

<i>RL</i>	Re-List
<i>RTA</i>	Road Traffic Accident
<i>SD</i>	System Dynamics
<i>SFPR</i>	Sickest-First Priority Rule
<i>SIRO</i>	Service in Random Order
<i>SU</i>	Super Urgent
<i>UKAM</i>	UNOS Kidney Allocation Model
<i>UKT</i>	UK Transplant
<i>ULAM</i>	UNOS Liver Allocation Model
<i>UNOS</i>	United Network for Organ Sharing
<i>WL</i>	Waiting List

Definitions

<i>Acute Liver Disease (ALD)</i>	A liver disease which last a duration not exceeding 6 months.
<i>Cadaveric Donor</i>	A person who has recently died and permission has been given to use his or her organs for transplantation.
<i>Chronic Liver Disease (CLD)</i>	A liver disease which last a duration of longer than 6 months.
<i>End Stage Liver Disease (ESLD)</i>	Liver disease (acute or chronic) which has progressed to a life threatening stage and the only option is for the patient to receive a liver transplant, otherwise they will die.
<i>Graft Failure</i>	Graft failure is when the implanted graft (here the transplanted liver) becomes damaged and stops functioning.
<i>Incremental Cost Effectiveness Ratio (ICER)</i>	The ratio of the change in costs of a therapeutic intervention (compared to the alternative, such as doing nothing or using the best available alternative treatment) to the change in effects of the intervention.
<i>Immnuosuppression</i>	Suppression of the body's natural defence (immune) system, which is necessary to prevent organ rejection.
<i>Living Donations</i>	Where a segment from the liver of a healthy person is taken and transplanted into the patient.
<i>MELD Score</i>	Measures the severity of chronic liver diseases; the higher the score, the higher the priority for transplantation.
<i>Routine/Elective</i>	Classification for patients who are not expected to die within 72 hours if they do not receive a transplant.
<i>Super Urgent (SU)</i>	Classification for patients who are expected to die within 72 hours if they do not receive a transplant.

Chapter 1

Introduction

1.1 Introduction

This chapter sets the background for the work performed in this thesis. It describes the UK Liver Transplantation System and identifies specific issues which provide the motivation for this study. These issues are discussed in detail and form a basis on which later chapters will build.

1.2 Background to the Liver Transplantation Problem Area

This section explains the need for liver transplantation, identifies the shortfall in the supply of liver transplants with respect to the demand for liver transplants in the UK, and considers the expected future trends.

1.2.1 What Does a Liver Do?

The *liver* is the largest organ inside a human body and it performs many functions that are essential to life, such as making bile to help with the digestion of food, filtering poisonous chemicals (including alcohol and drugs), and manufacturing proteins that the body needs to stay healthy and grow (The American Liver Foundation 2003a).

1.2.2 What Can go Wrong?

There are many types of liver disease which are capable of compromising the liver's function to the extent of threatening a patient's life. Diseases of the liver fall into two main severity groupings, referred to as *Chronic Liver Disease* (CLD) and *Acute Liver Disease* (ALD). The definition of an Acute Liver Disease is based on the duration of the disease not exceeding 6 months, while liver diseases of longer duration are classified as Chronic Liver Diseases (Richardson and O' Grady 2002).

Acute Liver Diseases have a more rapid onset than Chronic Liver Diseases and the most common causes of Acute Liver Disease in Europe are acute Hepatitis A, acute Hepatitis B, and reactions to recreational or therapeutic drugs.

Fibrosis is the damage of healthy liver cells which are then replaced by scar tissue. If left untreated, the liver can become so seriously scarred that it cannot heal itself. This stage is called *cirrhosis* (The American Liver Foundation 2003b). Cirrhosis is a consequence of many chronic liver diseases and interferes with the flow of blood through the liver and also the many functions of the liver.

A list of the most common liver diseases has been compiled by UK Transplant¹ and is provided in Appendix A (Section A.1.1).

¹ UK Transplant coordinates organ matching in the UK and is responsible for allocating donated organs in an unbiased and fair way (UK Transplant 2007).

1.2.3 Treatment

If a chronic liver disease is diagnosed at an early stage then in most cases the damage to the liver can be stopped or reversed through the use of medication and/or a change in diet (The American Liver Foundation 2003b), and the liver can regenerate itself (Court *et al.* 2002). However, the liver is a non-complaining organ and many people with liver diseases or disorders often experience no symptoms (The American Liver Foundation 2003a). Once a patient's liver disease (whether acute or chronic) has progressed to a life threatening stage then the patient is said to have *End Stage Liver Disease* (ESLD). At this stage no alternative currently exists and either a patient obtains a transplant or they will die (The Hepatitis C Trust 2006).

Liver Transplantation is the replacement of a diseased liver with a healthy liver allograft. A liver transplant operation removes all or a portion of the diseased liver and replaces it with a whole liver, or a reduced liver or segment (Parents of Kids with Infectious Diseases 2006). Liver transplantation is effective at prolonging survival and improving the quality of life of patients with end stage liver disease (Bambha and Kim 2003).

Patients awaiting a transplant fall into two groups depending on the severity of the disease, and whether or not there is an immediate threat to life. Patients who are expected to die within 72 hours should they not receive a transplant are deemed *Super Urgent* (SU). *Routine/elective* patients are expected to die within 1 year and there is no immediate threat to their life (Scottish Executive 2006).

For the future, several artificial-liver systems are being developed and tested to help treat patients with liver disease. In particular, plasmapheresis and the molecular adsorbent recycling system are two techniques which have provided promising initial results against acute liver disease (Hayes and Lee 2001; Hessel *et al.* 2002). Their development has, however, been limited due to the relative rarity of acute liver failure. Xenotransplantation (using organ grafts from animals in humans) may also become possible in the future (Talbot 2003; Strong 2001), while research into the potential for injecting healthy cells from donated livers directly into patient livers is also showing promising signs. As the healthy liver cells regenerate, the patient's dysfunctional liver cells are replaced with new healthy ones. There is hope that this technique could help the 20-40 children (who receive priority for liver transplantation over adult patients) currently obtaining liver transplants every year, and in turn free up the supply of livers so that more adults may benefit from a transplant. Although many new technologies are being researched, liver transplantation is currently the only reliable treatment for people with badly damaged livers.

1.2.4 Scale of the Problem (The Demand) and Donations (The Supply)

To the year ending 31st March 2006 there were 868 new registrations (including re-registrations for second or subsequent transplants) onto the UK liver transplant waiting list (UK Transplant 2006). Over the same time period 612 livers were donated and 601 liver transplants took place. The number of patients present on the liver transplant waiting list on the 31st March 2006 was 365.

The Demand

The size of the waiting list gives an indication of the demand for liver transplants but the true extent of this demand is likely to be much larger. Firstly, it has been acknowledged that patients in need of transplantation may not be placed on the waiting list if it is thought they are unlikely to receive a transplant (ETHOX). Secondly, a study by Sherwood *et al.* (2001) concluded that abnormal results for liver function are often not adequately investigated, missing an important chance of identifying treatable chronic liver disease. In other cases it has been found that general practitioners have been unable to establish what is wrong, meaning that many diseases may be left undiagnosed (Walsh 2004).

It is also difficult to measure unmet demand by analysing the number of deaths due to liver disease as it will not always be mentioned on death certificates, especially if there was more than one cause of death.

The Supply

The vast majority of UK liver transplants, 98.5% in the year ending 31st March 2006, come from *cadaveric donors* (UK Transplant 2006). Death can occur in two ways: (1) from heart-lung function stopping, and (2) from brain function stopping. Donors from the first group are classified as non-heart-beating donors and the latter group are classified as heart-beating donors. Heart-beating donors are more commonly used for transplantation, as they lead to higher success rates than non-heart-beating donors (University of Edinburgh).

Living donations can also be carried out by taking a segment from the liver of a healthy person and transplanting this into the patient (The American Liver Foundation 2003c; Mutimer 2002). This is possible because of the ability of the liver to regenerate, meaning that both the segment and the remaining section of the donor liver will grow to normal size within weeks. The Human Organ Transplant Act 1989 allows living donations so long as no commercial arrangements are involved (Neuberger and Price 2003). Adult-to-child living liver transplants have been performed in the UK and in April 2006 the first adult-to-adult living liver transplants were made available to patients on the NHS in Scotland (UK Transplant 2005a). The first adult-to-adult living liver transplant was performed in England in June 2007 (BBC 2007). However, due to the relatively high donor morbidity and mortality risks involved in donating livers in this way, in the past the UK Government were reluctant to allow this technique to be widely used. The risk of complications to the donor is 19% (compared to 1% for kidney donors) and the risk of death up to 1% (compared to 0.03% for kidney donors) (MacGilchrist 2004; UK Transplant 2005a). Living donations and the ethical issues related to this are discussed in more detail in Section 1.5.2.

1.2.5 Gap between Demand and Supply

The number of patients waiting for a liver transplantation currently outweighs the number of livers donated for transplantation.

Table 1.1 New Registrations, Outcomes and Liver Retrievals for the Year Ending 31st March 2006 (UK Transplant 2006).

Total number of patients (on the waiting list at 31 st March 2005 and new registrations between 1 st April 2005 - 31 st March 2006)	1152
Number of liver transplants²	601 (52%)
Number of deaths	89 (8%)
Number of removals	83 (7%)
Number of livers retrieved	612
Number of retrieved livers used	551

From Table 1.1, it can be seen that 89 patients died whilst on the waiting list for a liver transplantation; this represents nearly 8% of the number of patients that were present on the waiting list that year. Another 7% were removed from the waiting list and most of these will have been removed due to their health deteriorating to the extent that their chances of survival post-transplant were not strong enough to warrant the procedure. Note that no central record is kept about patients who were removed from the waiting list, but life expectancy for these patients is very low. The general shortage of organs for transplantation has been reported in many places, including by the Parliamentary Office of Science and Technology (2004).

1.2.6 Future Trends

The Demand

Although the general need for liver transplantation is increasing, it is hard to specify need in absolute terms due to the reasons discussed in Section 1.2.4.

² The number of liver transplants is greater than the number of donations used since a donated liver may be split between two recipients.

However, some cause and effect relationships have been identified for the main liver diseases and are outlined below.

Deaths due to end stage liver disease are increasing. Figure 1.1 gives an indication of the increases over the 34 years prior to the year 2004. In 2001 the Chief Medical Officers (CMOs) report in 2001 concluded that there was a great concern about the growing prevalence of Chronic Liver Disease, and the implications for the future.

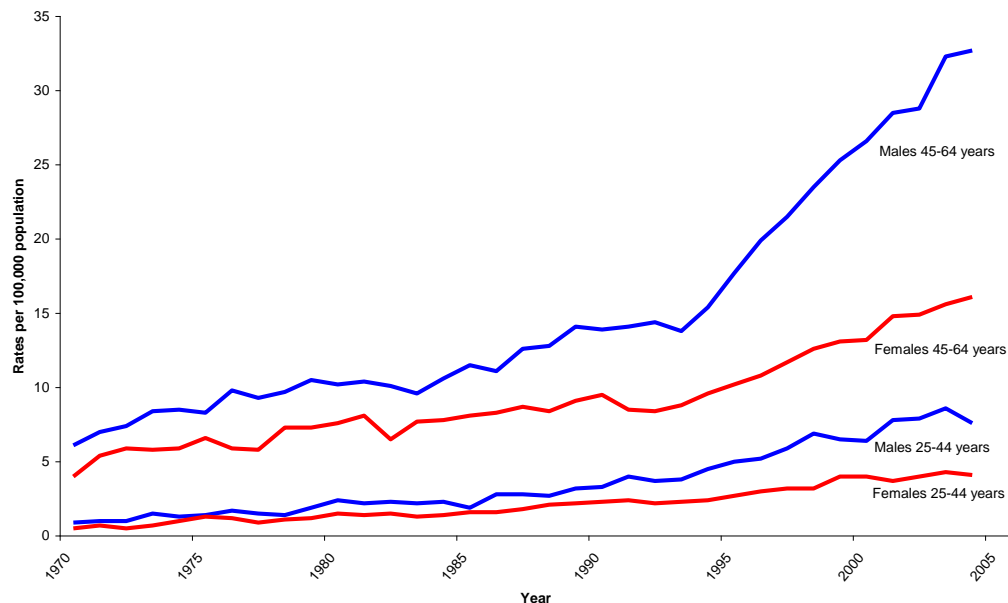


Figure 1.1 Death rates due to chronic liver diseases from 1970 to 2004 (Office for National Statistics; cited by CMO 2001).

A report on the emerging trends in chronic liver disease and the impact on demand for liver transplantation (Roderick *et al.* 2004) identified three chronic liver diseases which are likely to increase in prevalence in the near future, and hence increase the demand for liver transplantation. These are: Hepatitis C, Non-Alcoholic Fatty Liver Disease (NAFLD), and Alcoholic Liver Disease.

There is a high prevalence of Hepatitis C among injecting drug users. Roderick *et al.* (2004) applied Australian predictions to the UK, which indicated between a 2.5-fold and 4-fold increase in CLD burden from Hepatitis C over the next two decades. Given the time lag in the evolution of cirrhosis from initial Hepatitis C Virus (HCV) infection this prediction is independent of the number of current injecting drugs users and the current rate of HCV infection.

For NAFLD they found that the epidemic of obesity and Type 2 diabetes will lead to increased incidence of NAFLD. They predicted that whilst the majority of cases will have benign disease a proportion will progress through to Non-Alcoholic Steato-Hepatitis (NASH) and onto cirrhosis (Roderick *et al.* 2004).

The Office for National Statistics has reported that the number of deaths in England and Wales where the underlying cause was directly related to alcohol (such as liver disease and alcohol poisoning) has risen by nearly a fifth (18.4%) between the years 2000 and 2004 (BBC 2005). In 2001 the annual report from the chief medical officer highlighted that there is a worrying trend in the number of teenagers who drink alcohol and the quantities they consume (CMO Report 2001), which has led to liver cirrhosis striking at younger ages. The high level of alcohol intake in the UK, particularly among younger age groups has led Roderick *et al.* (2004) to conclude that the prevalence of alcoholic liver disease will continue to rise.

Demand is increasing for other reasons too. A greater number of patients are suitable and eligible for liver transplantation due to better operative techniques and earlier diagnosis (Parliamentary Office of Science and Technology 2004). Improvements in surgical techniques and new immunosuppression regimens have also enabled the treatment of patients who have a less promising prognosis (Neuberger 1999; Neuberger 2003). Hepatitis B and Hepatocellular cancer are two diseases which have recently seen significant improvements in post transplantation survival and there have been calls to allow more patients with such diagnoses onto the waiting list (Gow and Angus 2002).

A reduction in the size of paracetamol packs, which was imposed in September 1998, has led to fewer cases of acute liver diseases following attempted overdoses (Prince *et al.* 2000; Hawton *et al.* 2001). Overall, however, the trend in the number of people suffering from End Stage Liver Disease (ESLD) is clearly upward.

The Supply

The blue bars in Figure 1.2 depict the number of livers donated per year between 1996 and 2006. It can be seen that the donation figures have remained more-or-less constant over the last 10 years. This is in spite of several government aided awareness campaigns which have been targeted at the general public to increase the donation rates.

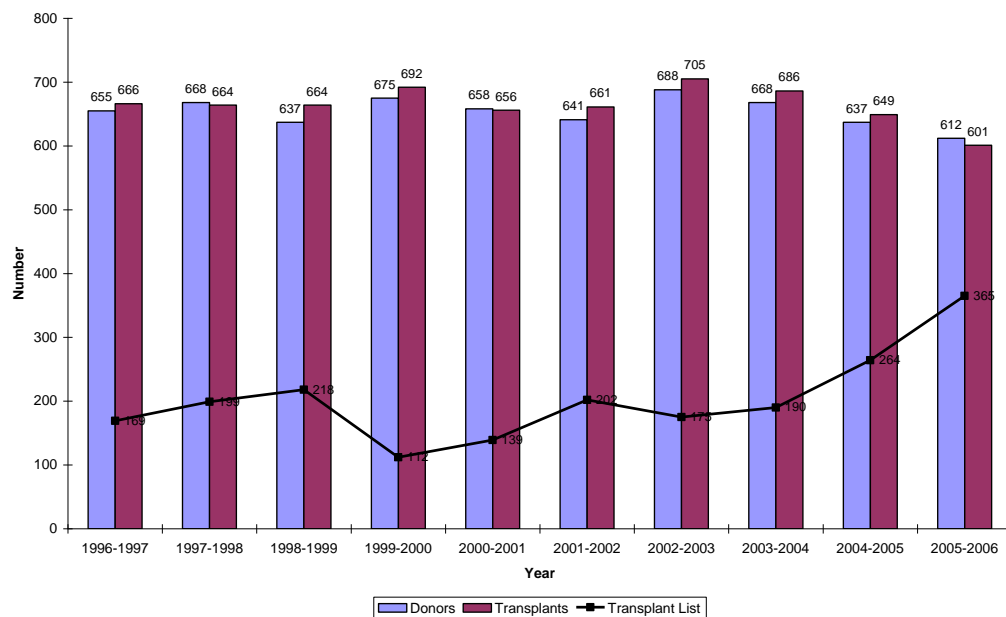


Figure 1.2 UK Cadaveric liver programme, 1st April 1996 – 31st March 2006: Number of donors, transplants and patients on the active transplant list at 31st March (UK Transplant 2006).

The National Health Service (NHS) Organ Donor Register (ODR), which is held by UK Transplant (UKT), was set up in 1994 to collect the names of members of the public who are willing to donate their organs after their death (UK Transplant 2004a). UKT has increased the number of people on the ODR from 8 million in 2001 to 13 million in March 2006 through awareness campaigns, such as driving licence applications, reminders through the Driver and Vehicle Licensing Agency, general practitioner registration and Boots Advantage Card applications (UK Transplant 2006; Parliamentary Office of Science and Technology 2004).

Increasing the number of people on the ODR is one thing, but they can only become potential donors once they die. At the same time as attempting to increase donation rates, Government initiatives have succeeded in reducing the

number of fatalities due to road traffic accidents (RTAs), which has led to a reduction in the number of donations made in this way. Improvements in paramedical care, neuro-surgical practice, and preventative medicine (such as treatment of hypertension) (Parliamentary Office of Science and Technology 2004) are also likely to have had an impact on the donation rate. As a result of these countervailing effects, the number of donations has not increased as might have been hoped.

ABO-compatibility has an immediate effect on whether or not a transplanted organ is rejected by the recipient's body. (The compatibility rules for the donor and recipient's blood groups are defined in Appendix B, Section B.1). People from different ethnic groups tend to have different blood groups so it is important to have donations from all ethnicities to ensure the equity of the system.

Table 1.2 shows the number of donors and recipients from different ethnic groups, with the disparity in the Asian population very pronounced. To address this, in 2003 the Department of Health launched a South Asian Organ Donor ad campaign to encourage more Asians to become donors (Media Moguls 2003). The impact appears to have been minimal, with the number of Asians requiring a transplant far outweighing the number who have donated livers in 2005/6.

Other examples of recent campaigns are those targeted at students, black members of the public, and one as a part of the celebrations of the 10th anniversary of the NHS ODR (UK Transplant 2004c).

Table 1.2 Ethnicity of liver donors and recipients, 1st April 2002 – 31st March 2004 and transplant list patients at 31 March in the UK (UK Transplant 2004c).

2002-2003						
	Donors		Transplant Recipients		Active and Suspended Transplant List Patients	
	N	(%)	N	(%)	N	(%)
White	675	(97.5)	598	(84.0)	143	(79.0)
Asian	7	(1.0)	74	(10.4)	17	(9.4)
Black	4	(0.6)	10	(1.4)	1	(0.6)
Chinese	2	(0.3)	4	(0.6)	3	(1.7)
Other	4	(0.6)	26	(3.7)	17	(9.4)
Not Reported	3	-	0	-	0	-
TOTAL	<i>695</i>		<i>712</i>		<i>181</i>	
2005-2006						
	Donors		Transplant Recipients		Active and Suspended Transplant List Patients	
	N	(%)	N	(%)	N	(%)
White	594	(95.7)	520	(85.2)	309	(84.7)
Asian	6	(1.0)	56	(9.2)	34	(9.3)
Black	10	(1.6)	15	(2.5)	8	(2.2)
Chinese	0	(0.0)	4	(0.7)	0	(0.0)
Other	11	(1.8)	15	(2.5)	14	(3.8)
Not Reported	0	-	0	-	0	-
TOTAL	<i>621</i>		<i>610</i>		<i>365</i>	

Although registering as an organ donor helps to express your willingness to donate after death, current practices require that the family of the potential donor must give consent for organ donation, regardless of whether or not the deceased had been on the Organ Donor Register (UK Transplant c.1999). A further discussion of the donation system follows in Section 1.5.1.

UK Transplant regularly carries out audits of potential donors. One audit report, considered all patients who died in an Intensive Care Unit (ICU) between 1st April 2003 and 31st December 2005. Potential heart-beating donors are defined as those for whom death was diagnosed following brain stem tests and who were judged suitable for organ donation. Figure 1.3 shows that only 46% of these 3,707 potential donors actually became organ donors. 85% of relatives were approached, but 39% of these refused to give consent for organ donation (UK Transplant 2006).

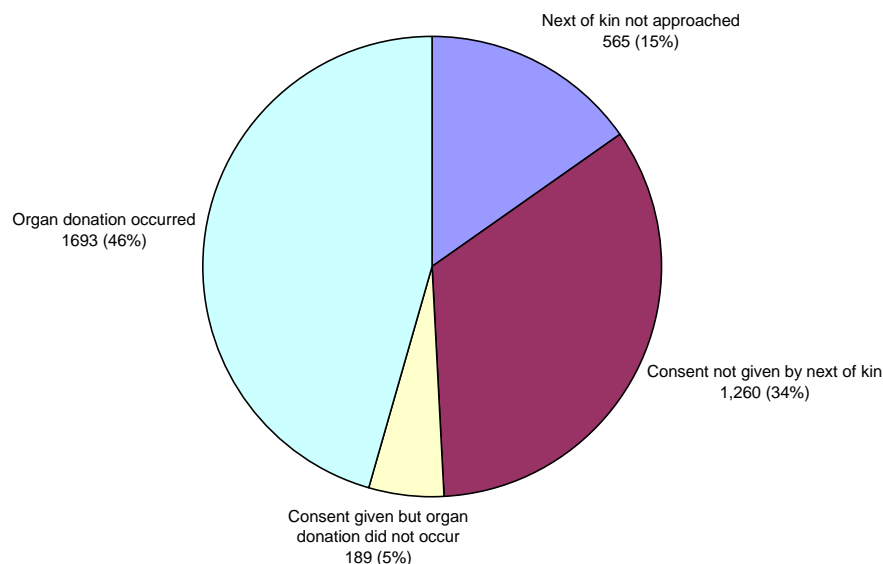


Figure 1.3 Percentage of UK Deaths Resulting in Organ Donation for the period 1st April 2003 - 31st December 2005.

Following the 2003/04 audit, UKT provided more detail in their report (Allen *et al.* 2004). The most significant finding was that non-white families were far less likely to give consent for donation than white families (refusal rates for the two groups were 77% and 36%, respectively). They were also slightly less likely to be approached in the first place. Other key factors were the time at which the

family was approached and whether or not a Transplant Co-ordinator was involved in this approach.

Organ donation rates have remained steady for a number of years, and there is little indication that the supply of donated livers is likely to increase in the near future (Neuberger 1999).

1.2.7 Summary of Demand and Supply Issues

The number of people requiring a liver transplant is increasing (Neuberger 1997; Neuberger 1999) but despite government awareness campaigns (Neuberger 2003; UK Transplant 2004b), the supply of livers in the UK has remained fairly constant (UK Transplant 2006).

The supply of donated livers currently does not match the demand and this shortage is likely to continue, or even increase in the future as it is predicted that the number of people requiring liver transplants (particularly for Chronic Liver Diseases) will increase.

One of the key motivations for this study arises from this inequality, and the resultant need to utilise the available donations as effectively as possible.

1.3 Liver Transplantation in the UK

The first human liver transplant was performed in Denver, USA in 1963 and the first in the UK was performed at Addenbrooke's Cambridge in 1968 (UK Transplant 2004d). Since then, many patients have benefited from the procedure. In the UK in the year to end March 2006, 601 liver transplants were performed (UK Transplant 2006).

Healthcare in the UK is mainly provided through a publicly funded NHS. This section briefly outlines the aims of the NHS, explains how liver transplantation fits into NHS care, and outlines a few specific issues concerning liver transplantation.

1.3.1 The National Health Service

Any public health service attempts to improve the health of the people it cares for. It does this at various stages of the natural disease progression: prevention (education and immunisation), early detection (screening and blood tests), and through the provision of treatment (drugs and operations).

The UK NHS was set up in 1948 with the main aim of providing universal, comprehensive and free healthcare for all UK residents. It still remains the main provider of healthcare to the population of the UK and is now the largest health service in Europe (National Health Service).

Over the last 59 years it has experienced many changes, ranging from the setting in which it operates and the type of patients it cares for, to the management of its resources. The NHS was established just after the Second World War, when society on the whole was used to amenities being rationed, whereas today it operates in a consumer based society where knowledge of different treatment options is easily obtained, e.g., through internet websites. Patients are therefore more likely to know about many of the options that exist and to demand what they see as the right treatment for them.

Offering patients more choice in the treatment they obtain is just one challenge that the NHS has had to meet in recent years (BBC 2006). Another challenge concerns the ailments that the NHS must care for. Initially, the focus concentrated on finding treatments and many issues revolved around providing acute care. Partly as a result, the population is now on average living longer; hence more are likely to experience chronic diseases, such as coronary heart disease, cancer and diabetes. The good news is that in general chronic illnesses can be managed and most patients can continue to live a life of reasonable quality. In many cases chronic illnesses are preventable, through leading healthy lifestyles (exercise, diet, not smoking).

In recent years more of the focus of the NHS has shifted from treating illnesses to preventing them. In 2004, the government published a white paper entitled “Choosing Health” (Department of Health 2004), which focused on many of the issues concerning healthcare now and in the future. It set out an agenda for the

future which included opportunities “for everyone to make their own individual informed healthy choices” as this will play a key role in helping to prevent chronic diseases in the future.

1.3.2 Liver Transplant Centres

Currently, liver transplants for adults on the NHS can only take place in one of seven liver transplant units in the UK, which are listed in Table 1.3.

Table 1.3 Liver Transplant Units in the UK (British Liver Trust).

Region	Hospital
East Anglia	Addenbrooke’s, Cambridge
N E Thames	Royal Free Hospital, London
Northern	Freeman Hospital, Newcastle Upon Tyne
S E Thames	King’s College Hospital, London
West Midlands	Queen Elizabeth Hospital, Birmingham
Yorkshire	St James’ Hospital, Leeds
Edinburgh & Lothian	Edinburgh Royal Infirmary, Edinburgh

In general, each liver transplant unit is responsible for procuring organs and transplanting patients within a particular region of the England (and Ireland), as depicted in the map presented in Appendix C.

There are a few exceptions in that other (non liver) transplant units are not necessarily based in the same hospitals and sometimes is it easier for one hospital to procure all organs from a particular donor. Also, patients may occasionally be registered at a hospital outside of the region in which they reside, however at any one time they can only be registered at one hospital.

If no patients on the UK Transplant waiting list are suitable or available for transplantation, then the donated liver will be offered to patients registered privately within the UK or to patients waiting for a liver transplant in the rest of Europe.

1.3.3 Falling ill with ESLD to Receiving a Liver Transplant

Figure 1.4 shows the main stages a patient goes through, from falling ill with ESLD to obtaining a liver transplant (from a cadaveric donor). Once ill with ESLD, the patient is referred to a liver unit where they are assessed for transplant suitability (Section 1.3.4). If they are judged suitable then they are placed on the UK liver transplant waiting list and wait until a suitable liver is donated and allocated (Section 1.3.5) to them, at which point they are transplanted.

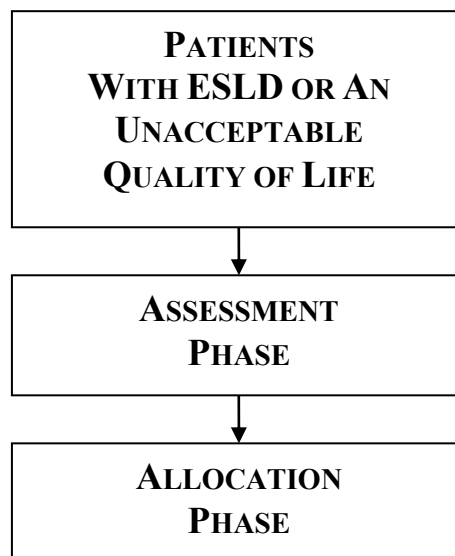


Figure 1.4 Process from a patient falling ill with ESLD to transplantation.

The three key stages in the process depicted in Figure 1.3 are: (1) the diagnosis of patients either with ESLD or with liver disease and an unacceptable Quality of Life (QoL)³, (2) the assessment phase, and (3) the allocation phase.

Changes in the criterion of any one of these stages will have a direct impact on the number and the type of patients within the liver transplantation system. The next two sub-sections detail how the assessment and allocation phases are currently implemented in the UK.

1.3.4 Assessment Process

The assessment phase is the stage at which a decision, subject to pre-defined suitability criteria, is made as to whether or not a patient should be placed onto the transplant waiting list. Various tests and interviews are carried out to determine how much the patient is likely to benefit from a transplant. The current suitability criteria for transplantation are documented and are designed to ensure that the number of patients on the waiting list remains in balance with the number of donors and to encourage consistency between units (UK Transplant 2001a). The guidelines broadly define the criteria as:

- (A) The patient has an anticipated length of life (in the absence of transplantation) of less than one year, or an unacceptable quality of life;*
and

³ In this thesis Quality of Life refers to Health Related Quality of Life (HRQoL). HRQoL is how a person's health affects their ability to carry out normal social and physical activities. The values this measure can take on range from 0 (inactive/dead) and 1 (full functionality). HRQoL is measured using patient questionnaires.

(B) They have greater than 50% probability of survival at 5 years after transplantation with a quality of life that is acceptable to the patient (Devlin and O'Grady 1999; Neuberger and James 1999; UK Transplant 2001a).

These criteria are evaluated by the teams within the seven separate liver units (as listed in Table 1.3). Due to the degree of subjectivity, the criteria are dependent on the interpretation of the unit at which the patients are assessed. The unmet need is hard to quantify, as there may be little data available about the patients that are rejected. Also it is not known how many patients would be suitable for a transplant but are not referred to a transplant centre, perhaps because the chances of being placed on the waiting list and being allocated a transplant are too small.

Post transplant survival rates are improving due to advances in care during and post transplant, (UKTSSA c.1995), and therefore more patients are likely to satisfy criterion (B).

There are some reasons which are outlined in the protocols as to why a patient may be less likely to be judged a suitable candidate for liver transplantation. These reasons include alcohol-induced liver disease, illegal drug use, self-inflicted conditions, medical and psychiatric conditions, regrafts, malignancy, and disease progression to a state where criterion (B) is no longer satisfied as the

patient is too ill to survive the transplant. The age of the patient is also taken into account when determining their suitability for transplant.

1.3.5 Allocation Process

Once patients join the waiting list they are essentially in competition for the donated livers. In the UK, patients must have a compatible blood type to the donor's blood type, if they are to be allocated the donated liver (UK Transplant 2002a). Other factors taken into account are weight matching, matching based on donor and patient risk groupings, and the geographical location of the patient compared to the donated liver.

Figure 1.5 details the allocation process as it is currently implemented. When a liver becomes available, if any children (aged 16 years or younger) with a compatible blood group are waiting for a liver transplant then they are considered first to receive the donated liver. Next, the waiting list is checked for any compatible super urgent patients. If there are any then the donated liver is allocated to one of them. If not, then the nearest centre (usually the retrieving centre) checks whether or not they have a suitable routine candidate. If they do not then the liver is offered to other centres, based on a balance of exchange system. The balance of exchange system attempts to make sure that the number of liver transplants a centre performs roughly matches the number of liver retrievals they make.

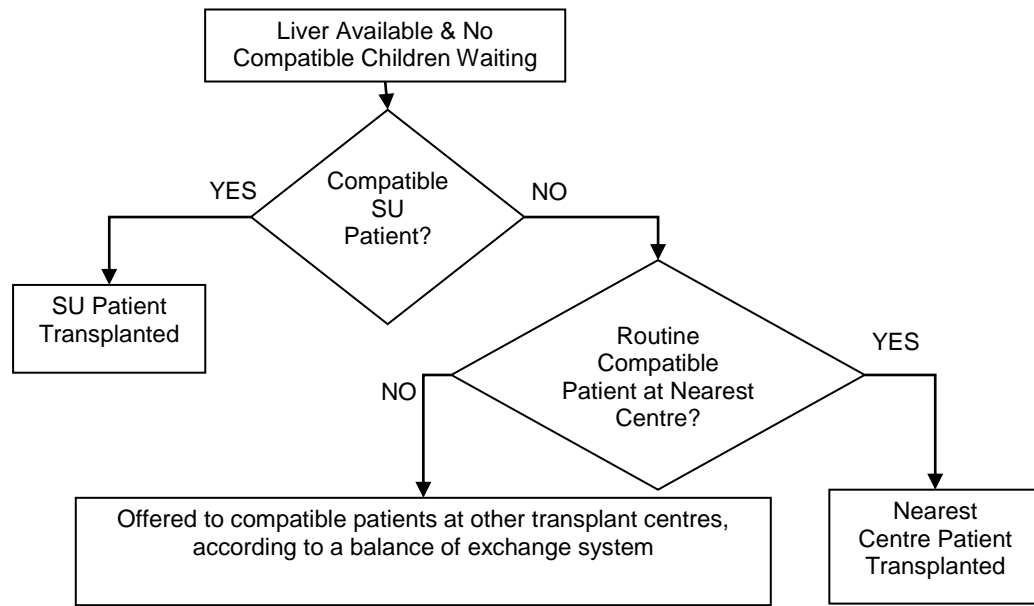


Figure 1.5 A Flow Chart to Represent the Current Liver Allocation Rules.

1.4 Ethical Issues in the Allocation System

There are a number of ethical aspects associated with the transplantation of livers, which may influence future demand.

1.4.1 Cost-Effectiveness of Liver Transplantation

A liver transplantation costs in the region of £40,000 and the cost of *immunosuppression* treatment for a patient post transplant is roughly £6,500 a year for the rest of a patient's life (BBC 2003; Medical News Today 2004). Immunosuppression is the artificial suppression of the immune system, so that the body will not reject a transplanted organ or tissue.

A recent study found that all organ transplantation is generally cost-effective, particularly in relation to NHS spend. The exception that they identified was the

cost-effectiveness of liver transplantation as a treatment for alcoholic liver disease (Longworth *et al.* 2003; UK Transplant 2003a), due to a larger number of patients being assessed in this group and not being put forward for transplant.

1.4.2 Assessment for Liver Transplantation

There is some debate around who should be eligible for liver transplantation. Issues include the likelihood that the disease will recur post-transplant and whether or not the disease was preventable.

Recurrence of Disease

Following transplantation some diseases can recur and damage the replacement liver, notably Hepatitis B and Hepatitis C (Gow and Angus 2002; UK Transplant 2001a). A study in Western Australia found the overall rate of disease recurrence to be 10% in a particular cohort of patients (Yusoff *et al.* 2002). The rate of recurrence was seen to vary significantly between the indications for transplantation, with a recurrence rate of 40% in patients initially transplanted for Hepatitis B (Rosen 2001). There are also restrictions currently in place which do not allow patients with tumours greater than 5cm in size or with more than 3 tumours to proceed to the transplant waiting list (Devlin and O'Grady 1999). There is much debate on whether these criteria are too restrictive. On the other hand, it could also be argued that patients without such complications might benefit more from a donor liver.

Preventable Diseases

The high profile case of George Best has kept the debate of transplanting patients with preventable diseases, alive (Scotsman 2004). As the Government attempts to focus their resources more on preventing chronic diseases it is important to consider whether patients with preventable liver disease should receive the same priority for liver transplantation as those with non-preventable liver disease. One argument considers the likelihood of compliance to post transplant treatment. A study considering sobriety, drug-compliance and adherence to appointments for Alcoholic Liver Disease after liver transplantation, found that most patients were compliant but relapse to drinking occurred in 13% of recipients. A patient's return to alcohol consumption post transplant is associated with rapid development of histological liver injury including fibrosis, meaning that they potentially require another transplant (Tang *et al.* 1998). Alcoholic liver disease patients also reported poorer health-related quality of life post-transplant compared with other patients (Longworth *et al.* 2003; UK Transplant 2003a).

1.4.3 Allocation of Liver Transplants

There are many conflicting viewpoints and ethical issues surrounding the transplant allocation process. Several other studies have also attempted to assess various stakeholder viewpoints. A survey published in 1998 (Neuberger *et al.* 1998) questioned the general public, family doctors and gastroenterologists (within the UK) about their views concerning the allocation of donated livers to potential recipients of liver allografts. They established that the priorities of the

public differ from those of the medical profession. The public tend to prioritise on a more emotional basis and rank patients with antisocial behaviour (alcohol, drug users) lowest. Whereas, the doctors and gastroenterologists consider overall outcome, work status and the likelihood of working post transplant as key criteria when allocating the livers.

A study in Australia (Browning and Thomas 2001) concentrated on obtaining the views of the general public on how organ allocation decisions should be made. They too found that the public prioritise emotionally with the factors of younger age and being a parent being key in their decision making. Other factors that they find to be significant are better prognosis post-transplant and the length of time spent waiting for a transplant.

Ratcliffe (2000) performed a survey to investigate the nature of public preferences to the allocation of donated livers for transplantation. She interviewed both academics and non-academics from a British University. The survey results indicate that most members of the surveyed group thought that the post transplant survival chances should be the main deciding factor in the allocation of transplants. However, when faced with a choice situation in which there were a limited number of donor organs to allocate between two groups of individuals with differing characteristics, the overwhelming majority of respondents chose not to abandon the group with the lower expected survival.

It is extremely important for public views to be acknowledged within the decisions made through the transplantation process as they donate their organs to make transplantation possible, and if the system does not portray what they wish for then they may be less willing to donate.

1.5 Ethical Issues in the Donation System

There are a number of ethical aspects associated with the transplantation of livers, which may influence future supply.

1.5.1 Opt In or Opt Out

Currently the UK operates an informed consent (opt in) system for organ donation, whereby individuals are asked to register their willingness to be a donor after their death (UK Transplant c.1999). In practice, relatives of the patient are always consulted and asked to give explicit consent. If the relatives cannot be found, or they refuse to give consent, then organ donation cannot take place, even if the deceased had been on the ODR.

Shortages in the number of donations (as discussed above in Section 1.2.5) have led to debates on whether a system of presumed consent would be more appropriate. Under this system it is assumed that an individual wishes to be a donor unless they have “opted out” by registering their objection to donation after their death. The British Medical Association, many transplant surgeons, and some patients’ groups and politicians are keen to change the current system.

(BBC 2004; Kennedy *et al.* 1998). They argue that although the presumed consent system may make little difference to short term donation rates it will affect the culture and framework within which discussions about donation will take place and oblige everyone to consider whether or not they wish to donate their organs after death and to discuss this with their close relatives (Parliamentary Office of Science and Technology 2004).

Table 1.4 Legislation, practice and donor rates (Source: Council of Europe; National Transplant Organisation; cited by Parliamentary Office of Science and Technology 2004).

Country	Legislation	Actual Practice	Donors (per million people) Annual Rate 2003
Spain	Presumed Consent	Informed Consent	33.8
Belgium	Presumed Consent	Presumed Consent and Family Informed	24.4
Austria	Presumed Consent	Presumed Consent	23.3
US	Informed Consent with Required Request	Informed Consent with Required Request	22.1
Ireland	Informed Consent	Informed Consent	21.1
Norway	Presumed Consent	Informed Consent	19.2
France	Presumed Consent	Informed Consent	18.3
Netherlands	Informed Consent	Informed Consent	14.9
Germany	Informed Consent	Informed Consent	13.8
Sweden	Presumed Consent	Varies, Recent Changes	12.8
UK	Informed Consent	Informed Consent	12.0
Greece	Presumed Consent	Informed Consent	6.4

Some arguments for presumed consent stem from the organ donation rates observed in different countries. Table 1.4 shows donation rates by country and

the policy in place. Spain which has the highest donation rates (almost 3 times as many donations as the UK) has presumed consent legislation in place, however in practice operates a system of informed consent – in that relatives are asked whether or not they are in favour of donation (Parliamentary Office of Science and Technology 2004).

Studies comparing the Spanish and UK donation systems in more detail found a number of additional factors that could account for the relatively high donation rates in Spain. Firstly, it should be noted that there are double the number of deaths from road accidents in Spain, greatly increasing the pool of potential donors. There are also significantly lower refusal rates from patient relatives (20-24%) compared with 39% in the UK. (UK Transplant 2003b; 2006). Refusal rates by patient relatives in the UK have increased from 30% in the early 1990s to 42% in 2004. Many factors could be responsible for this increase including the Alder Hey (English and Sommerville 2003) scandal in 1999 where organs were kept without consent. Support from the Catholic Church may also have an impact on donation rates in Spain (Parliamentary Office of Science and Technology 2004). Finally, the high donation rate in Spain is thought to be mainly due to the way organ donation is co-ordinated, with a national network of specially trained physicians in charge of the whole process of organ donation. The UK has fewer transplant co-ordinators than Spain, despite having a larger population, and it is thought that the lack of a ‘transplant culture’ in hospitals is also an issue.

The Department of Health (2002) is not in favour of a change in legislation to that of presumed consent and has not found any evidence that the public would overwhelmingly support presumed consent from responses to its *Human Bodies, Human Choices* consultation. It maintains that changing the legislation would be a high risk strategy and believes that without clear public support it may lead to reduced donation rates. Currently the level of public support for changing the system is unclear, a poll carried out in 1999 by the Department of Health reported that 50% of respondents favoured the current system, 28% supported a shift to presumed consent and 22% expressed no preference (UK Transplant c.1999).

In June 2004 it was decided in Parliament that the decision as to whether or not to donate should be left to the individual (Scotsman 2004).

A more recent survey (Lyll 2005) carried out by the BBC (or their TV Programmes *Holby City* and *Casualty* identified three main fears the UK public had with regards to donating their organs after their death:

- (1) Mis-use: organs taken without consent (possibly due to instances like Alder Hey - where organs were taken without permission (English and Sommerville 2003));
- (2) Doctors will be too keen to turn off life-support, so that others may benefit from your organs; and
- (3) Accuracy of the brain-stem test in determining whether or not someone is dead.

1.5.2 Living Donations

Living donor liver transplantation for adults was developed as an attempt to increase the pool of donor organs (Shiffman *et al.* 2002). Most living donors are relatives of the patient due to the importance of providing a good match between donor and recipient. This is one of the main limiting factors for this technique, while further complications arise from medical contraindications in the donor (Neuberger and Price 2003).

Neuberger and Price (2003) believe that living liver donation should be recommended for patients who are eligible to receive a liver graft but who have a high probability of death or clinical deterioration that would preclude transplantation before a cadaveric graft became available. The Royal College of Physicians of Edinburgh agree but extend their criteria to include patients with hepatocellular carcinoma, where delaying the operation will increase the risk of extra-hepatic spread (MacGilchrist 2004).

Initially, there was doubt about the use of living donors, especially after one donor died in the US (Josefson 2002). Since then, research has helped to improve understanding about the ideal donors and recipients for this procedure (Tan *et al.* 2005) and many hope that living donations will help to ease the chronic shortage of organs currently experienced worldwide. Factors that may reduce the risks associated with the procedure are: selecting younger donors (<45 years old), placing allografts in recipients who have not had a prior transplant and who are not in the Intensive Care Unit (Abt *et al.* 2004).

1.5.3 Marginal Livers

There is no specific definition of a marginal liver (Neuberger c.2004). Many authors use the definition that a marginal organ is one where there is a risk of initial poor function or primary non-function. Neuberger suggests some characteristics of a marginal liver donor as including: older age, high Body Mass Index (BMI), steatosis, brain stem death, and prolonged Intensive Treatment Unit stay. Other reasons include partial liver grafts, and grafts from non-heart beating donors. Other factors include technical factors such as warm and cold ischaemic times and recipient factors, and particularly factors regarding the closeness of the match (blood group and ethnicity) with the donor. The shortage of organs has led to American transplant centres expanding their criteria for the acceptance of marginal donors (Busuttil and Tanaka 2003). Similarly in the UK the use of marginal livers has been expanded, Table 1.5 below depicts the increased use of marginal livers in the UK, figures were obtained from UK Transplant data (UK Transplant 2004e).

Table 1.5 Marginal Liver Characteristics (UK Transplant 2004e).

Donor Characteristic	1999	2000	2001	2002
Donor Age < 65 years	95.1%	94.5%	93.7%	92.0%
Donor Age >= 65 years	4.9%	5.5%	6.3%	8.0%
Whole Liver	87.6%	88.1%	87.6%	87.0%
Split/Reduced Liver	12.4%	11.9%	12.4%	13.0%
Cadaveric heart-beating donor	100%	100%	99.8%	99.7%
Cadaveric non heart-beating	-	-	0.2%	0.3%

There appears to have been an increase in the use of marginal livers (donor age greater than or equal to 65 years, split/reduced livers), and the potential for increasing the number of transplants that could be carried out is significant. It is

estimated that an increase in the use of non-heart-beating donors may give rise to a 25% increase in the number of organs donated within the UK (Patient UK c.2005). The ethical considerations still remain, however, due to the poorer survival rates associated with marginal livers.

1.6 Summary

There are several key reasons for why there is a need to create a model of the UK liver transplant system. These include the gap between demand for liver transplantation and the supply of livers from the cadaveric donor pool and the many conflicting view points concerning various ethical aspects of the system. Considering future trends of demand and supply the gap is likely to increase, in particular, due to the increasing number of people falling ill with chronic liver disease. The scarcity of this resource makes it important to allocate the donated livers effectively.

There are two key stages within the UK liver transplantation process which influence who will eventually be given a liver transplant operation. These are the assessment phase (at which point criteria define if a patient meets the requirements to join the waiting list), and the allocation phase (at which point patients on the waiting list are prioritised for an available liver transplant operation). The allocation stage and patient assessment stage are complex and act as taps that control patient flow through the system, based on the policies in place.

Many ethical considerations which support the need for a model to be created, also exist. The issues are wide-ranging, however, can be grouped into three main areas: equity, utility and operational issues. Equity and utility issues are at the heart of debates concerning who should obtain a liver transplant (e.g., cost-effectiveness seeks to maximise utility potentially at the expense of equity; restrictions on transplants for patients with recurring diseases or patients with preventable diseases would again affect utility and equity; and direct changes to the allocation rules can affect both equity and utility). Operational issues also exist: some doctors believe that an opt out system would provide a greater number of donations, however, politicians think that the decision to donate should be left up to members of the public. The use of marginal and living donations is increasing to help alleviate some of the demand, but although new technologies are being developed, it will be some time before they can be used widely.

Chapter 2

Literature Review

2.1 Introduction

This chapter examines the present tools used to explore transplant assessment and allocation decisions, summarises the existing literature and discusses the applicability of present techniques within the UK liver transplantation problem area.

The chapter ends by summarising the main findings of the literature search and formulating the research objectives and questions of the work contained in the rest of this thesis.

2.2 Transplant Matching Studies

Allocation policies for two types of transplant - liver transplantation and renal (*kidney*) transplantation - have been investigated extensively. This section identifies the reasons why the modelling of allocation policies is worthwhile and summarises the models which have previously been developed, highlighting their key components.

2.2.1 Reasons to Model Liver and Renal Transplantation Systems

Ninety three percent of all patients registered for a transplant in the UK on 31st March 2006 were registered for either a liver transplant or a renal transplant (UK Transplant 2006).

The three main characteristics of both transplant systems which make the investigation of various allocation policies worthwhile, are:

- (1) The shortage in the donations of both types of organs, compared with the demand for transplants. In the year ending 31st March 2006, the number of deaths from the liver and renal transplant waiting lists were 89 (8%) and 286 (3%), respectively (UK Transplant 2006);
- (2) The size of the waiting lists (which means there will generally be a choice as to which patient to allocate a donated organ to); and
- (3) The long organ preservation times, increasing the number of options available to clinicians in terms of how the available organ could be allocated. (The liver can be preserved for around 12-18 hours after removal from the donor, while a kidney can be preserved for 24-48 hours. This is in contrast to about 6 hours for most other organs (UNOS 2004).

The number of similarities between liver transplantation and renal transplantation mean that similar modelling approaches can be applied to both systems. There are however two additional factors which are important to consider in renal transplantation. Firstly, an additional factor when matching a patient with a donor kidney is Human Leukocyte Antigens (HLA), which have

been shown to be important in post transplant graft survival (Claas *et al.* 2004; Opelz 1988). Secondly, dialysis is also an option for patients with renal failure, which means that patients can survive without a transplant, although renal transplantation offers a far better quality of life. As a result, it becomes important to compare Quality Adjusted Life Years (QALYs)⁴ when investigating different kidney allocation policies.

2.2.2 Comparing UK and US Systems

Many liver and renal studies have modelled the systems within the USA. However, differences exist between the two countries which mean that these studies are not directly applicable to the UK systems. Clinicians in the USA have to consider the issue of distance between where an organ is procured and where it is taken to be transplanted (UNOS 2004). The travel times between procurement and transplant must respect the preservation times mentioned above (in Section 2.2.1) to ensure initial graft functionality post transplant. In the UK the distances are not as great and all travel times fall within the 12 hour lower limit for liver preservation.

Another issue present in the USA is that the patient can choose whether or not to accept a donated organ (UNOS 2004). This issue arises from the fact that Americans pay either directly (to the transplant centre) or indirectly (through

⁴ A QALY is a measure that combines both morbidity and mortality. The measure is based on utility theory which values full health as 1 and death as 0. Some conditions, like persistent severe vegetative state, may be given negative utilities. If someone with a utility of 0.75, for example, has an extra four years of life, then they have three QALYs whereas a completely healthy person (with a utility of 1) would have 4 (Davies *et al.* 2003).

medical insurance) for their transplant and those who cannot afford to pay do not receive a transplant. In paying for medical provisions patients are more likely to reject an organ which may be marginal (Section 1.5.3) and may instead opt to wait for their next offer which may be an organ of higher quality. The initial offer indicates that they have reached the top of the waiting list, and that an alternative donor organ is likely to be offered soon. The rejection of organs gives additional time pressures to the US system. In the UK, there is more of an expectation that people will accept any organ allocated to them and as a result fewer donations are rejected.

The registration criteria in the USA are less strict than the process in the UK as patients in the USA are able to join more than one transplant centre waiting list, improving their chances of obtaining a transplant (UNOS 2004). In addition, US patients can join a waiting list as soon as they are diagnosed with liver disease. Hence the US models have concentrated on attempting to capture natural history data in great detail. In the UK, however there are stricter assessment rules (Section 1.3.4) and patients must be expected to die within a year before they may join the waiting list, therefore a UK model does not need to replicate the detailed natural history models created in the USA.

Another difference is that the US model incorporates the Model for End stage Liver Disease (MELD) score (see Section 3.7.1 for a detailed definition) in the decision as to which patient should be allocated a liver transplant (UNOS 2004). The MELD score measures the severity of chronic liver diseases; the higher the

score, the higher the priority for transplantation. In the UK, MELD scores are collected but are not used in the national allocation of liver transplant operations.

2.2.3 Previous Transplant Matching Studies

This section summarises the main models which have been created to represent the liver and renal transplant systems in the USA and the UK.

Liver Transplant Matching Models

Roberts (1992) developed a model to help to understand the optimal time at which to offer a transplant to a patient. He used Markov processes to describe the transitions between different disease states and evaluated the strength of different selection criteria by using Monte Carlo Simulation. The key outcome analysed was the life expectancy of the patient and this was measured using survival analysis. The difficulty with the modelling approach he took is that it only considered the selection strategy used by *one* US transplant centre to estimate if a transplant increased survival over the natural history and he was only able to consider the outcomes that had occurred at that transplant centre.

Howard (2001) compared various basic allocation policies. The allocation rules which were investigated are: sickest-first priority rule (SFPR), first-come first-served (FCFS), and service in random order (SIRO). He simulated the arrival of donors and patients and assessed the impact of the different policies against a measure of patient survival and health post transplant, while also considering the fairness of the policies at allocating equally to patients with an urgent need for a

transplant, and those with a less urgent need. The main finding was that compared to a FCFS queue or SIRO, a ‘sickest first’ policy resulted in worse patient outcomes when the demand-to-supply ratio is high. The model however failed to capture several of the key factors within the US transplant system which would affect the success of transplants carried out, including the following: locations of procurement and transplant and the transport times between them, re-transplantation, and organ (weight and blood group) matching. The main limitation was that of insufficient data which made it hard to extend the model to incorporate all the regions within the USA.

UNOS Liver Allocation Model (ULAM) (Harper *et al.* 2000; Pritsker, A *et al.* 1995; Pritsker, A *et al.* 1996) is the simulation model used by the United Network for Organ Sharing (UNOS), a tax exempt, medical, scientific and educational organisation that operates the national Organ Procurement and Transplantation Network (OPTN), in the US. The main motivation in building ULAM was to compare proposed liver allocation policies on a national basis, at a time when the number of patients on the waiting list was growing faster than the number of liver organs being donated. A suite of outcomes are considered to assess different policies, ranging from the relative survival rates of patients, to the fairness of the system created.

The model created incorporates features that are present in other models such as initial waiting list composition, patient and donor arrival streams, allocation policies, and mortality and re-listing rates post transplant. Additional issues the

model attempts to deal with include medical urgency status which changes as a patient's illnesses progresses, liver offer/acceptance rates, and increasing survival rates post transplant (that would result from better immunosuppression medication regimens, drugs available pre-transplant, and advancements in transplant techniques). The model has been accepted by clinicians as a result of their involvement in its creation. Although the model does consider medical urgency, it does not look at the causes of liver failure and how these affect the overall outcomes. ULAM also does not attempt to make predictions concerning future demand and supply (e.g., the anticipated increase in the number of Hepatitis C cases, discussed in Section 1.2.6).

More recently, a group from Pittsburgh (Kreke *et al.* 2002a; Kreke *et al.* 2002b; Shechter *et al.* 2005) have developed a more robust model based on ULAM, which attempts to allow the inclusion of inputs that are not influenced by the current policy. Their approach has been to separate the modelling of the biology and natural history of the disease from the allocation and selection mechanism. They managed to prove the concept of modelling the biology and natural history of a liver disease by validating a model which incorporated a separate disease progression module and a survival module (with and without transplant), to predict the time-course of individual patients as they progress through their disease, and estimate pre- and post- transplant mortality and re-transplantation. The outputs of the model included survival times, cost, waiting time information and information on the number of wasted organs. They acknowledge several limitations, the most important being that the natural history module is based on

data from a single site (the University of Pittsburgh Medical Center UPMC), whose patients are not representative of the national population. Another important limitation Kreke *et al.* (2002a) acknowledge is that the proportional hazards assumption (as detailed in Section 2.4.1) which is assumed by the Cox models may not be satisfied (Kreke *et al.* 2002a). Alagoz *et al.* (2005) have continued working on this model to develop more realistic approximations in capturing the changes in clinical characteristics of patients with end-stage liver disease to be used to calibrate the natural disease progression model.

A group from Brunel (Baldwin *et al.* 2000; Eldabi *et al.* 2001) have developed the only model of the UK liver transplant allocation system, with the motivation to evaluate the cost-effectiveness of liver transplantation for the Royal Free Hospital liver unit, and to assess whether an alternative allocation policy would be more cost-effective. Their model (LiverSim) incorporated expected outcomes with, or without transplant and reflected the patterns of care that would be obtained in both circumstances. A Discrete Event Simulation model was created to model a patient's progression through the assessment, candidacy (on the waiting list) and transplant phases, and the cost associated with each phase. They evaluated Incremental Cost Effectiveness Ratios (ICERs) for several policies (including priority to patients with high/low waiting times, high/low patient age, high/low clinical severity, and various clinical severity groupings). Their results identified that the cost-effectiveness of liver transplantation is improved by giving priority to younger patients and those least severely ill, when compared to the policy that was in place at the time.

The main limitations of the LiverSim model, are:

- Only two liver diseases were considered (alcoholic liver disease and primary biliary cirrhosis);
- Super Urgent patients were not included; and
- Quality of Life (QoL)/Quality Adjusted Life Years (QALYs) were not evaluated.

Although the two most common diseases (representing 30% of the adult patients who joined the UK liver transplant waiting list between 1999 and 2002) were considered these are not necessarily representative of the less common diseases, in terms of costs. Super Urgent patients are also important since they take priority over other patients and generally incur substantial ICU costs over a few days pre-transplant. QoL/QALYs are also important for use in establishing the cost-effectiveness of Liver Transplantation, since QALYs are a standard measure used to evaluate the benefit of treatment by NHS/DoH, therefore considering ICERs alone is not sufficient (Austin 2007).

A later study by Longworth *et al.* (2003) considered midterm cost-effectiveness in terms of the costs per QALY. Again they only considered a limited number of liver diseases (those for which prognostic models were available: primary biliary cirrhosis (PBC), alcoholic liver disease, and primary sclerosing cholangitis (PSC)). The disease groupings investigated represented 37% of the patients who joined the UK liver transplant waiting list between 1999 and 2002. They found that PBC and PSC were cost-effective, however, alcoholic liver

disease was less cost-effective, in part due to the higher number of alcoholic liver disease patients assessed for each transplant.

Renal Transplant Matching Models

In the USA, the UNOS Kidney Allocation Model (UKAM) (Taranto *et al.* 2000) is a model that is being developed following the success of ULAM. The motivation in developing UKAM was to enable the evaluation of various cadaveric kidney and kidney-pancreas transplant allocation policies. The model is very similar to ULAM but has been developed to take into account the main differences between the two systems, such as the use of dialysis to treat patients awaiting a transplant. A Markov transition matrix has been constructed to model how a patient's sensitivity to donor antigens changes during the time they spend on the waiting list. The authors' hope is that UKAM like ULAM will be able to provide a means of helping people navigate through the complex issues involved in the allocation of donated kidneys.

Another model in the USA that compares various kidney transplant allocation policies has been developed by Zenios *et al.* (1999; 2000). They used Monte Carlo Simulation to measure the relative equity of policies across different age, gender and ethnic groups; while considering the relative efficiency of different policies in terms of patient survival and quality-adjusted life expectancy. The model also incorporated HLA matching rules and blood group compatibility between patients and donors. An area where the model could be made more

robust is in identifying factors which influence mortality on the waiting list and in graft survival post transplant.

Key Components to Define as Identified from Previously Developed Transplant Matching Models

From the previously developed transplant matching models, three areas have been identified that require defining and modelling in order to capture the current liver transplant assessment and allocation system and to provide a basis for the evaluation of alternative assessment and allocation policies. These are:

- (1) The identification of suitable measures for comparison between policies;
- (2) The identification of a technique by which to estimate the time a patient remains in a particular state; and
- (3) The identification of a methodology by which to model patient progression through the system.

These areas are discussed over the next three sections and appropriate Operational Research (OR) and Statistical methodologies, and their strengths and weaknesses are evaluated. Examples of where the methodologies have previously been used within health services are also outlined.

2.3 Identifying Suitable Model Outcomes

Liver transplantation is the only treatment available for End Stage Liver Disease (ESLD) and as already identified there is a shortage in the number of donated livers with respect to the number of patients requiring liver transplants (Section

1.2.5). The challenge for clinicians when choosing an allocation policy for donated livers is to yield the best patient outcomes (be the most effective), while being fair to all patients (encouraging equity amongst all patient groups) (UK Transplant 2005b).

2.3.1 Equity (Fairness)

Equity measures convey the overall fairness of the liver allocating system in allocating livers across different patient groups. To ensure equality and fairness, everyone should have equal access to organ transplantation (Douglas 2003).

Neuberger *et al.* (1998) found that members of the public are willing to exchange an overall reduction in the efficiency of the transplantation system for a fairer or more equitable means by which to allocate donated livers to patients on the waiting list. The American Medical Association has defined certain criteria by which it is unacceptable to select patients for organ transplantation (Douglas 2003), which aid to ensure equity amongst the different patient groups.

These are:

- (1) Ability to pay;
- (2) Contribution of the patient to society;
- (3) The behavioural contribution of the patient to his or her medical condition;
- and
- (4) The past use of medical resources.

In the UK there are no formal rules, however, the selection protocols for liver transplantation have been designed so that they should not discriminate against a patients' assessment for transplantation by any of the above points (Section 1.3.4).

Equity measures may be represented in various ways (e.g., as waiting times, or the percentage of patients transplanted within groups), across a range of categories (e.g., disease type, geographical region, gender, age, ethnicity) (Pritsker *et al.* 1996). The figures obtained for each equity measure must be of comparable magnitude across all groupings to resemble a fair policy. For the system to be fair, it has to be fair at every stage:

- (1) Falling ill to referral - which patients are referred to the liver units by their General Practitioners;
- (2) Referral to joining the waiting list - which patients are judged suitable for transplantation;
- (3) Waiting list to transplant - which patients are allocated a donated liver; and
- (4) Transplant to re-listing - which patients from those that require another transplant, are actually re-listed.

Equity in the first of these stages is often the hardest to evaluate since the number of patients who are referred to a liver unit may only represent the *tip of the iceberg*, and there may be very little information available about patients who are never referred (as discussed in Section 1.2.4).

2.3.2 Utility (Effectiveness)

Utility measures help us to determine the overall benefit gained under a particular allocating system (UK Clinical Ethics Network 2004).

Surveys have shown that most physicians who perform transplants believe that patients should be treated solely on their capacity to survive and benefit, regardless of the cause of their organ failure (Ghent 1996; cited by Douglas 2003). Neuberger *et al.* (1998) confirmed that doctors and gastroenterologists regard utility as a key driver when allocating donated livers.

Neuberger (2003), argues that selection of patients for listing should be based on utility. He acknowledges that there are discriminatory factors with applying a utility based approach, he however argues that these are acceptable because they are based on objective and validated risk factors. Examples are given to indicate why allocation should not necessarily be 'fair', when determining the most efficient allocation policy. These include:

- A 70-year-old is less likely to receive a graft than a similar 40-year-old; not because of their age but because older age is associated with a worse outcome (Garcia 2001; cited by Neuberger 2003); and
- An alcoholic person or drug user with ESLD may not be offered a liver transplant; not because of why they developed liver disease but because there is a good chance that they will not comply with post-transplant treatment, leading to a recurrence of liver disease.

Since there is no alternative treatment to liver transplantation for ESLD, an appropriate utility measure to assess the total benefit gained under a particular policy is the total *Life Years* (LYs) gained. The LYs gained represents a straightforward measure of the increase in survival under a certain policy, and is obtained from the calculation below:

$$\begin{aligned} E(\text{gain in LYs}) \\ &= E(\text{death time post - transplant}) \\ &\quad - E(\text{death time without transplant}) \end{aligned}$$

where $E(x)$ is the expected value of x .

The calculation of Quality Adjusted Life Years (QALYs) (Davies *et al.* 2003), normally provides a better indication of the actual use and impact of the healthcare resources but it requires collection of years of Quality of Life (QoL) data. It becomes more relevant when modelling the renal transplant system, as patients receiving dialysis can survive for some time without transplant, but experience a relatively poor quality of life. QoL is, however, a very subjective measure and would not necessarily provide a reliable means of finding the “best” policy, for patients with ESLD.

Process and outcome utility measures include the total costs incurred; the number of transplants performed; the number of donated organs that are wasted; and the number of patients to benefit from transplantation, or to suffer from graft rejection, or recurrence of liver disease. Utility measures indicate the overall impact of the policies and are designed to capture the overall effect that transplantation or non transplantation has. Again, to identify the true effectiveness of the liver transplantation system, utility measures must be

monitored at all stages, to identify the end outcomes of all the patients that could benefit from a liver transplant.

2.3.3 Balancing Equity and Utility

There are several concerns in using equity and utility measures. Normally, creating equity between patients will not maximise the utility of donated liver organs, and vice versa (Bleichrodt *et al.* 2004; Sassi *et al.* 2001). Therefore, there may be a need to balance these measures against one another. It is also important to take into account the opinions of different stakeholders within the liver transplantation system as they will have their own views about how patients should be prioritised (as discussed in Section 1.4.3).

2.3.4 Previous Transplant Matching Studies

Of the previous models, those concerned with effectiveness and cost-effectiveness tend to only consider utility measures. For example, LiverSim (Eldabi *et al.* 2001) considers the average LYs gained and the average costs for both the transplant and non-transplant processes (through the calculation of ICERs), and Roberts (1992) considers the average life expectancy of the patients under varying selection criteria in order to find the optimal time at which to transplant and hence utilise the donated livers most effectively.

The Pittsburgh model (Kreke *et al.* 2002a) measures QALYs, the costs spent on ESLD, the number of patient deaths while waiting, the average waiting time, and the number of wasted organs.

Zenios *et al.* (1999) include similar outputs (patient survival, QALYs, waiting time to transplant, and likelihood of transplantation) and considers them by selected patient groupings (ethnicity, gender, age less than or greater 50 years old). Zenios *et al.* (2000) consider the equity-utility trade-off in kidney transplantation and analyse how this trade-off can be alleviated.

All the other models also investigate both equity and utility. Howard's model (2001) contains a utility measure which is based on the loss of health transplanted patients experience which he defines as the difference between the actual 3-month graft success rate and the 3-month graft success rate if the patient were transplanted immediately after listing. He defines an inequitable policy as one in which patients listed in one health state receive a much greater probability of receiving an organ than patients listed in other health states.

The liver transplant model with the most comprehensive equity and utility outputs is ULAM (Pritsker *et al.* 1996). Within ULAM; medical, patient and system outputs are evaluated and compared between policies as outlined in Table 2.1. UKAM (Taranto *et al.* 2000) contains a similar range of both equity and utility measures.

Table 2.1 Measures present in the output module of ULAM (Pritsker et al. 1996).

Type of Measure	Measure
Equity	Total (non-repeating) transplants
	Probability of receiving a transplant (once on waiting list)
	Waiting time distribution from joining waiting list to transplant
	Probability of dying from the waiting list
	Waiting list size through time
Utility	Total (non-repeated) transplants
	Total other patients removed or died on waiting list
	Percent of transplanted patients that survive
	Total patients re-listed
	Size of the end waiting list
	Gain in Life Years (LYs)

Many of the previous models have concentrated on measuring the effectiveness (utility) of the system in using the donated livers, however, a few studies have also considered the equity-utility trade-off, to varying extents. The equity-utility trade-off is important within the UK liver transplantation system since most transplants are provided through the NHS and so there is a need that all taxpayers should receive an equal chance of transplantation, as well as a need to provide value for money (maximising utility).

2.4 Estimating the Time Spent in a Particular State

We need to identify a technique which allows us to estimate how long a particular patient will spend in a certain state before progressing to another state. The estimation of times is a key aspect of the modelling of the liver transplantation system. It will determine the rate at which people die from the waiting list and the rate at which patients are re-listed post-transplant. A realistic representation of the liver transplant waiting list is crucial to the

accuracy of the model and in ensuring that the allocation policies are implemented correctly. Being able to estimate the expected times to both pre-transplant events (such as death) and post-transplant events (such as death and *graft failure*⁵) will also enable us to calculate the additional life years gained by a patient from receiving a transplant.

The most appropriate statistical inference techniques for this purpose are survival analysis or competing risks analysis. Survival analysis and competing risks analysis concern the modelling of data where the variable of primary interest is the time interval (T) between some specified origin and an event of interest occurring. Table 2.2 outlines the events of current interest and the corresponding origins.

Table 2.2 Events of Interest within the Liver Transplantation System and the Corresponding Times of Origin.

Event of Interest	Time of Origin
Death or Removal from the waiting list	Time joined the waiting list
Death or Graft Failure post transplant	Time of transplant
Re-listing post transplant	Time of transplant

Survival data cannot be modelled through common statistical procedures used in data analysis (Collett 2003), such as linear and multiple linear regression, because:

- (A) *Survival times are generally not symmetrically distributed.* Data will tend to be positively skewed, i.e., if a histogram of times is plotted it will have a longer “tail” to the right of the mode than to the left; and

⁵ Graft failure is when the implanted graft (here the transplanted liver) becomes damaged and stops functioning. As a result the patient will die within a day.

(B) *Survival times are frequently censored (not observed exactly)*. For example, when considering the outcome of “death or removal from the waiting list”, not all the patients who will experience this outcome will be observed to do so within the observation period of the study. Some will go on to experience death or removal after the study has stopped gathering data. This type of censoring is called *right-censoring* - the true survival time is “to the right of” (greater than) the time for which the patient was followed-up. Other reasons for having to censor data include patients being lost to follow-up or when the cause of death is unclear.

There are several types of models which exist in survival analysis and each make different underlying assumptions. The simplest models assume the Proportional Hazards (PH) assumption and where this assumption does not hold, Accelerated Failure Time (AFT) models need to be considered. The PH assumption implies that if viewed across time, one patient will always be α times more likely to experience a particular event than another patient. The AFT assumption implies that the chances of one patient’s survival diminishes β times faster than that of another patient. Both types of model are discussed in more detail below, in Sections 2.4.1 and 2.4.2, respectively.

One important assumption that all survival analysis models make is that the censored times for a particular event occur at random (i.e., the censored times are not due to a common cause) (Collett 2003). This assumption may not apply in the current situation, when modelling the time until death from the waiting

list. In this case, all patients who received a transplant and all those removed from the waiting list would have to be censored at the time that these events occurred. However, both events, particularly removals, are likely to be dependent on the health of the patient – which is likely to be relatively poor. Moreover, they are both likely to be dependent on the patient’s time to death – the event we are trying to model. In this case a more appropriate technique would be Competing Risks modelling (Hutton and Hemming 2006). Competing Risks (CR) modelling allows for the above aspects to be taken into account and enables several events to be modelled at the same time, meaning that the assumption about independence of events does not need to hold.

General Forms

For all forms of survival and competing risks modelling we have the option of developing non-parametric models and parametric models, to capture the underlying survival times. Parametric models are more efficient when embedded in a simulation model and are preferred over non-parametric models.

Ideally we want to model the distribution of survival time, T , as a function of several explanatory variables (patient, donor and system characteristics, as appropriate). Both survival models and competing risks models allow for this type of inference. The techniques that are used in selecting covariates for both types of model are similar to those used in linear regression and are described in Section 3.6.3 [B] (Collett 2003).

Definitions in Survival Analysis

When summarising survival data, there are four functions that are of interest:

(1) The *distribution function*, $F(t)$, which describes the probability distribution function of the survival times.

(2) The *survivor function* (*survival function*), $S(t)$:

$$S(t) = P(T > t) = 1 - F(t), \quad (2.1)$$

which is the probability that an individual survives beyond time t . $S(t)$ exists for non-negative values of time, t , is a continuous non-increasing function, and $S(0) = 1$.

(3) The *probability density function*, $f(t)$:

$$f(t) = \frac{dF(t)}{dt} = -\frac{dS(t)}{dt}$$

which represents the underlying distribution of the random variable T .

(4) The *hazard function*, $h(t)$:

$$h(t) = \frac{f(t)}{S(t)} = \lim_{\delta t \rightarrow 0} \frac{P(T < t + \delta t | T \geq t)}{\delta t} \quad (2.2)$$

which tells you how likely the event is to occur at (or around) a particular time t , given that the event has not occurred before then.

Kaplan-Meier Estimate

The *Kaplan-Meier Estimate* provides a non-parametric version of the survival function. To obtain the Kaplan-Meier estimate a series of time intervals is constructed such that one death time is contained in a particular interval and this death time is taken to occur at the start of the interval (Note: More than one death may occur at the start of a particular interval).

The Kaplan-Meier Estimate, $\hat{S}(t)$, of the survival function is then given by:

$$\hat{S}(t) = \prod_{j=1}^k \left(\frac{n_j - d_j}{n_j} \right) \quad (2.3)$$

where n_j = the number of individuals who are alive just before time $t_{(j)}$

(including those who are about to die at this time),

d_j = the number who die at this time.

A large amount of computer space and processing would be required to use the Kaplan-Meier estimate for sampling purposes. However, plotting Kaplan-Meier estimates can give an indication of the underlying distribution of the survival functions, and this provides a useful way of comparing survival between different groups. More detail about Kaplan-Meier estimates and an example of its application are provided in Appendix D.

The observed hazard function can be used to determine which statistical modelling technique is the most appropriate to use. The appropriate survival model for various forms of the hazard function are summarised in Appendix E.

2.4.1 Proportional Hazard Models

Basic Definition

The *Proportional Hazards* (PH) assumption implies that one patient will always be α times more likely to experience a particular event than another patient. This is true of the hazard rates for patients j and k in Figure 2.1 below.

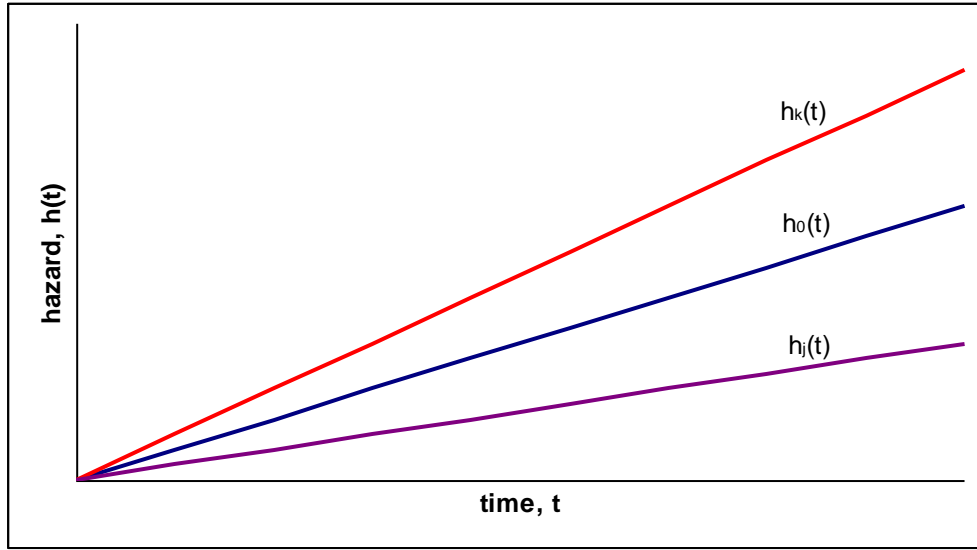


Figure 2.1 Hazard functions depicting the proportional hazards assumption.

Method

The PH model (Cox regression model) is the most general survival regression model because it is not based on any assumptions concerning the nature or shape of the underlying survival distribution. The model assumes that the underlying hazard *rate* is proportional to various combinations of the independent variables (covariates) (Forster 2004). The hazard function, $h_i(t)$, for some individual, i , with a set of explanatory variables defined as $\mathbf{x}_i = (x_{i1}, \dots, x_{ip})^T$ can therefore be expressed by the following equation:

$$h_i(t) = \exp(\mathbf{x}_i^T \boldsymbol{\beta}) h_0(t) \quad (2.4)$$

where $\beta = (\beta_1, \dots, \beta_p)^T$ is a vector of regression coefficients and $h_0(t)$ is called the baseline hazard function.

The most commonly used parametric versions of the PH model use Exponential, Weibull and Gompertz distributions to describe the survival time distributions. Non-parametric versions of the PH model can also be created; these assume that the *baseline hazard function*, $h_0(t)$, is non-parametrically modelled.

Advantages and Disadvantages

Authors like to use proportional hazard models because the base distribution is the same for all the covariates, and the risk over time changes between covariates by a constant factor. This allows for clearer assertions to be made (e.g., a patient with characteristic A will always be 3 times more likely to die than a patient with characteristic B) and a clear method of application. Another advantage of the proportional hazard model is that no functional form is imposed on the baseline hazards (Ahn 1994). This is very useful, especially in situations where the hazard function fluctuates a number of times. Proportional hazard models are easily fitted, as routines exist in many standard statistical packages (Goldstein and Harrell c.1996).

A disadvantage arises in that relatively few probability distributions are available for the modelling of survival times within the proportional hazards modelling approach (Collet 2003), and the distributions that are available require

the hazard function to increase or decrease *monotonically*⁶. There are however, numerous situations in which it is expected that the hazard function will change direction. For example, following a heart transplantation a patient faces an increasing hazard of death over the first ten days or so after the transplant, while the body adapts to the new organ and medications. The hazard then decreases with time as the patient recovers. Another disadvantage is that the model assumes that there is always a constant proportional difference between the hazards experienced by two individuals (e.g., patient i will always be α times more likely to experience death, compared to patient j), which may also be an unrealistic assumption.

Examples

Proportional hazards modelling has been used in a number of situations, ranging from reliability applications to healthcare applications.

Crowley and Hu (1977) were one of the first to use survival analysis techniques that incorporated several covariates in approximating post heart transplant survival. They considered the following covariates and created an exponential PH model to predict post transplant survival, (factors found to be significant are marked by an asterix):

- Transplant status *;
- Waiting time to transplant;
- Calendar time of transplant;

⁶ A monotonic function is one which is either strictly increasing or decreasing (i.e., does not change direction).

- Age at acceptance onto the waiting list;
- Age at transplant *;
- Previous open-heart surgery *; and
- Three measures relating to the tissue match between patient and donor *.

From this they were able to produce estimates for relative risks between groups and concluded that heart transplantation can prolong survival for certain younger patients if a suitably matched heart can be found.

Sohn *et al.* 2007, developed a Weibull survival model to help analyse the characteristics of employees who have longer occupational lifetimes (the length of time spent working for the same company). Their findings were that employees with the following characteristics had relatively longer occupational lifetimes:

- Those at the managing director level;
- Those who are relatively old;
- Those who entered the company earlier;
- High school graduates;
- Those who were involved in technical service; and
- Those married to female employees.

Kandinov *et al.* 2006 implemented the proportional hazards approach to evaluate the effect of cigarette smoking, tea and coffee consumption on the progression

of Parkinson's disease, and found that these variables do not have an effect on modifying the disease in patients already diagnosed.

2.4.2 Accelerated Failure Time Models

Basic Definition

The *Accelerated Failure Time* (AFT) *assumption* implies that although the shape of the survival curves are similar, one patient (patient i) will move along the survival curve β times faster than another patient (patient j), as depicted in Equation (2.5).

$$S_i(t) = S_j(\beta t) \text{ for all } t \geq 0 \quad (2.5)$$

Method

AFT models allow for non-monotonic hazard functions. They are less restrictive than PH models as they do not enforce the proportional hazards assumption, and the need for a monotonic underlying hazard function (Collet 2003). AFT model do, however, assume the same underlying survival curve for every patient and the only thing that differs is the speed at which the patient travels along the curve. In order to describe the underlying survival times there are several parametric forms of accelerated failure time models which are often suitable. These include: Weibull, Log-Logistic, Lognormal, Gamma and Inverse Gaussian. Note that for Weibull, PH and AFT are the same.

Advantages and Disadvantages

AFT models can cope with hazard functions changing direction, capturing both the increasing hazard in the days immediately following a heart transplant, and the decreasing hazard thereafter. Again many standard statistical packages include functions by which to fit AFT models (Goldstein and Harrell c.1996). AFT models take on parametric functions to describe the underlying survival times. For most of these functions is it relatively straightforward to perform Monte Carlo sampling in order to generate times by when a certain patient will experience a particular event within a simulation model. However, the interpretation of AFT models is less straightforward than for PH models.

Examples

Aitkin *et al.* (1983) considered data from the same transplant centre as Crowley and Hu (1977), their main aim being to determine whether survival improved for those who received a transplant compared with those who did not. They noted that the hazard of death initially increases post transplant for about 60 days and then declines after this. They too modelled survival time as a function of patients' attributes and transplant status but found the proportional hazards assumption was not satisfied by the data and so chose to fit AFT models instead. They compared various AFT models to those previously developed by Crowley and Hu and Kalbfleisch and Prentice (cited by Crowley and Hu 1977). They found that the underlying hazard function fitted more closely to the AFT models (lognormal, Weibull, piecewise exponential) than to the proportional hazards model established by Crowley and Hu (1977), previously. They also concluded

that the immediate short-term effect of heart transplant on survival was to increase the hazard, especially for older patients, however, the estimated long-term hazard appeared much lower for all patients post transplant. Their findings about different patient characteristics were that:

- Younger patients who received a transplant survived longer, especially those entering the program at an early stage;
- Age is significant as it affects survival post-transplant, but not pre-transplant;
- Calendar time is important because the pre-transplant survival improved markedly during the first 6 years of the program (which the data covered). This can largely be accounted for by improvements technology, transplant techniques/skills and practice; and
- Waiting time was found to be important because a declining hazard pre-transplant indicates a better prognosis for patients who have survived the initial waiting period.

Aitkin *et al.* (1983) were able to fit lognormal survival models to patients survival times, pre- and post-heart transplantation. Their aim in developing these models was to assess the effect of a heart transplant on the number of years a patient lived. However, they were unable to make any conclusive statements as they lacked information on the longer term survival of the non-transplanted group.

Lambert *et al.* (2004) managed to show that parametric accelerated failure time models can also capture in detail patient survival following kidney transplant.

2.4.3 Competing Risks Model

Basic Definition

Competing Risks (CR) can be used to model a situation where there is more than one type of outcome (e.g., there are a discrete number of possible causes of death) (Crowder 2001; David and Moeschberger 1978).

Method

The proportional hazards assumption described in Section 2.4.1 can be applied to CR models, by taking on a non parametric or Weibull baseline hazard function. Alternatively, CR models may also apply the AFT assumption (Section 2.4.2) by inferring non parametric, Weibull, Log-Logistic, Lognormal, Gamma, or Inverse Gaussian, forms for the survival function.

In CR the hazard function $h(j,t)$ for cause j is:

$$h(j,t) = \frac{f(j,t)}{S(t)} = \lim_{\delta t \rightarrow 0} \frac{P(T < t + \delta t, C = j | T \geq t)}{\delta t} \quad (2.6)$$

where T = the time to failure,

C = the cause of failure,

j = the cause (1... p),

$S(t)$ = the overall survival function,

$f(j,t)$ = probability distribution function of survival times to event j .

and the overall hazard function is given by:

$$h(t) = \sum_{j=1}^p h(j, t) \quad (2.7)$$

A simple test using the definition of the hazard function (which does not account for any type of censoring) as given in Equation (2.8), can help to determine if the censored times are independent of the cause. For a particular outcome i the hazard rate is defined as:

$$E_i(t) = \frac{n_i(t)}{N} \quad (2.8)$$

where i = the occurring event,

$n_i(t)$ = the number of events of type i that occurred at time t ,

N = the total number of patients observed.

Equation (2.8) is used to plot curves for each of the censored events that may occur (Hemming and Anzures-Cabrela 2006). For example, if we wish to model the time between a patient joining the waiting list and the patient's death, then we need to plot the hazard rate curves for the times which will need to be censored: (1) time to removal, (2) time to transplantation, and (3) time to suspension. If these curves are all of a similar shape and size, then the times to be censored are independent of cause and survival modelling is appropriate. If the curves differ in shape then each event needs to be modelled as an outcome and a competing risks model is more appropriate.

Advantages and Disadvantages

CR models are not commonly developed and do not appear in standard statistical packages.

CR models do not require the censored data to be independent from anything which causes them to be censored. If there is a specific cause of censoring then this can be included in the CR model as a separate event. This means that the overall estimates produced are less prone to bias caused by censored events.

Examples

Competing Risks models have been identified as an appropriate methodology for modelling many different aspects of reliability (Bedford), including the modelling of failure for two or more independent risks. Bailey *et al.* (2003) describe competing risks as an appropriate way in which to model the competing events which occur in the transplantation process: transplantation, death while awaiting the transplant, removal for other reasons, and death post-transplant. They stressed the need to consider these events in combination, rather than in isolation or one at a time.

2.4.4 Previous Transplant Matching Studies

Many of the previous transplant matching models have used survival models in varying degrees to approximate times to death (pre- and post-transplant) and graft failure post-transplant, a few of the most relevant are outlined below.

ULAM (Harper *et al.* 2000) uses non-parametric survival curves to estimate post-transplant mortality. These are stratified by a patient's medical urgency status at transplant, their previous transplant status, and the transplant centre volume.

The Pittsburgh model (Kreke *et al.* 2002a) also makes use of non-parametric survival distributions to approximate both the time to graft failure and death post-transplant. They implement Cox models based on the biological characteristics of the patient, the quality of the graft (transplanted organ) and patient-graft interactions at the time of transplant.

Eldabi *et al.* (2001) use prognostic models, which employed Kaplan-Meier techniques, in estimating survival with and without transplant which have been developed by Huges *et al.* (1992) for primary biliary cirrhosis and Anand *et al.* (1997) for alcoholic liver disease. They sampled appropriate survival times, based on the patient attributes captured in each of the models (Anand *et al.* 1997; Eldabi 2000; Huges *et al.* 1992)

Zenios *et al.* (1999) estimate the survival of patients on the waiting list by using constant hazard rate models split by age, sex and race. They estimate post-transplant graft and patient survival by using Kaplan-Meier techniques which are based on readily attainable covariates. These include covariates relating to:

- The patient (age, sex, race, height, weight, blood type, tissue type, diabetes, primary or repeat transplant, number of pre-transplant blood transfusions, peak and current panel reactivity, functional status);
- The donor (age, sex, race, blood type, tissue type, cause of death); and
- The transplant operation (kidney cold ischemic time).

2.5 Modelling Patient Progression Through a System

The different stages of a transplant system can be seen as a series of states which the patients progress through. There are two very different approaches that can be taken when modelling patient progression through a system:

- (1) Mathematical Modelling – Decision Trees; Markov models; and
- (2) Simulation of the system – System Dynamics (SD); Discrete Event Simulation (DES).

Both have their advantages and disadvantages and various studies which assess their advantages and disadvantages have been performed (Barton *et al.* 2004; Cooper *et al.* 2006; Cooper *et al.* 2007; Karnon 2002).

Decision Trees capture the different routes through the system, the probability of progressing down each of them, and the associated costs. By evaluating the decision trees it is possible to determine the probability of experiencing different outcomes, and the cost value of the outcomes. Cooper *et al.* (2007) found that decision trees were most commonly used to model short term interventions (e.g., diagnostic tests, thrombolysis and revascularisation). Markov models are based

on a similar concept, but with a time element to them; describing the probability of entities progressing from one state to another during a fixed time period. The evaluation of Markov models can yield the average time spent by entities in each state; and the associated costs and benefits of these (Cooper *et al.* 2007). Cooper *et al.* (2007) found that Markov models were commonly employed when considering long term interventions (e.g., statins and other drugs).

Simulation modelling can also take into account resource constraints in the system; along with any interaction between entities and resources. They are flexible techniques, modelling large periods of time very efficiently – a problem for Markov models. They can deal with variability, uncertainty, and can help to facilitate communication with, and comprehension by, healthcare professionals through the use of graphical interfaces (Brailsford and Hilton 2001). Two commonly implemented simulation techniques within healthcare are System Dynamics (SD) and Discrete Event Simulation (DES). Several studies attempt to compare various aspects of SD and DES methodologies. These papers highlight technical differences (Brailsford and Hilton 2001), conceptual differences (Lane 2000), and key differences in SD and DES approaches to problem solving (Morecroft and Robinson 2005).

The rest of Section 2.5 reviews the three techniques commonly applied to health care systems where costs are not the main emphasis – Markov Models, System Dynamics and Discrete Event Simulation. Their strengths and weaknesses are discussed, and examples of their use are provided.

2.5.1 Markov Models

Method

Markov processes are probabilistic models which form a special category of stochastic processes. Under this technique, events are modelled as transitions from one health state to another over a fixed time period. The transitions are determined by conditional probabilities and patients progress through the differing states until they reach an absorbing state, for example, death.

A key property of Markov processes is the *memory-less property*, i.e., the probability that the random variable X_t takes a particular value x_t depends only on x_{t-1} and not the previous values x_{t-2} , x_{t-3} , ..., x_0 . With regard to the transplantation system, this means that a patient's transition from one state of a disease to the next state depends only on the current state occupied and not on the previous history of the patient.

Advantages and Disadvantages

The memory-less property is unrealistic in the context of liver disease since a patient's medical history is likely to influence their future disease progression (e.g., re-listed patients may experience significantly different outcomes to those listed for their first transplant, and Markov models would not be able to incorporate this). Markov models also use fixed time cycles, which can lead to problems. If the time cycle is long compared with the frequency with which events occur then individual events cannot be captured at the exact time that they occur (Sonnenberg and Beck 1993). If shorter time cycles are used, then

time taken to process the model will be that much longer. This means that Markov models tend to be more useful for events that take place over long periods of time (Karnon and Brown 1998). They are also more effective when the hazard rate remains the same over time (Sonnenberg and Beck 1993). When looking at liver transplants, however, the chances of experiencing complications post transplant is much higher straight after the operation, and reduces thereafter (Collett 2003).

Semi-Markov models solve some of the issues raised above. They allow for extra states to be included in order to capture changes in risk over time. For example, one way to model changing risks would be to introduce two post transplant states. This of course assumes that there are two distinct states, with measurable risk levels associated with each. They can also be applied over varying time cycles, but the more states that are used, the more complex the model becomes, and the longer they take to evaluate.

Markov and Semi-Markov models are useful when considering simple chronic and long-term interventions and where the patients within the cohort under observation follow similar transition probabilities (Cooper *et al.* 2007). For these problems, such models are reasonably fast to run, are intuitive in their conception and can be very powerful for helping to enhance understanding of the systems that they model. As more and more assumptions are made about a system, the complexity of the Markov models can increase rapidly; becoming

very dense and losing transparency. Markov models can also be difficult to adapt to capture different scenarios.

Examples

Markovian methods have been applied in modelling various issues which emerge in healthcare. These include:

- Considering the progression of patients through intensive care units (Kapadia *et al.* 2000);
- Identifying the number of patients who are likely to enrol for a clinical trial (Felli *et al.* 2005); and
- Modelling the progression of coronary heart disease patients through various stages of their illness (Cooper *et al.* 2007).

2.5.2 System Dynamics

Method

System Dynamics (SD) is a deterministic technique that takes a holistic approach to modelling complex systems through a series of causal loops, which incorporate elements of feedback in the system. A simulation model is created to capture the flow of entities through the system over time, and this can be used to assess the overall impact of different policies. Mathematically, a SD model is made up of several sets of difference equations which attempt to define the flows between the stocks (e.g., to capture patient flows within the system),

where state changes are modelled as being continuous (Brailsford and Hilton 2001).

Advantages and Disadvantages

SD models combine both qualitative and quantitative techniques, and hence can capture various aspects of complex systems through the use of descriptive or judgemental information (i.e., expert opinion) as well as numeric data (Brailsford and Hilton 2001; Lattimer *et al.* 2004). This can also help in making the models understandable to a wider audience. By modelling feedback loops in the system they can incorporate highly dynamic relationships between different elements of the system, which are often ignored when specific processes are studied (Morecroft and Robinson 2005). As a result they are useful tools for developing an understanding about the entire system and are often used on a strategic level for evaluating the impact of different policy options (Brailsford and Hilton 2001; Lattimer *et al.* 2004; Morecroft and Robinson 2005).

SD concentrates on stocks of entities, rather than on modelling each individual separately. This does remove some of the complications when estimating the different parameters involved, particularly with regard the amount of data required to achieve this and the level of validation required. On the downside, this does also place restrictions on the usefulness and accuracy of the models. In particular, there is no way of evaluating how policies impact on specific individuals, or the length of time they spend in particular states (Lattimer *et al.* 2004). The complexity of the models is often limited by the complexity of the

difference equations at their heart, which can become unsolvable (Pidd 1992). SD does also lack the flexibility of other simulation techniques, particular in its modelling of the dwelling time in each state (Brailsford and Hilton 2001). Any simplifications made will ultimately impact on the mathematical accuracy of the results (Lattimer *et al.* 2004).

Examples

Evenden *et al.* (2005) created a system dynamics model to investigate the cost-benefit associated with screening intervention for the Chlamydia infection. They observed three patient groups – those susceptible to Chlamydia, those infected with Chlamydia, and those susceptible to sequelae (long term medical consequences) - and performed cost-benefit analysis to assess the viability of providing each group with the screening intervention. The modelling identified that prior infection did not lead to immunity from Chlamydia, hence that re-infection is a key characteristic in the long-term prevalence of Chlamydia. They were also able to conclude that the damage caused by infection increases the risk of sequelae (to up to 20%) and that sequelae costs were considerable. Risk groupings were defined based on the following attributes: transmission event, new partnership, and infected partner. They established that screening provides immediate cost benefits for both the high and low-risk groups. This was achieved through a reduction in the number of infections, as well as a long term reduction in costs of sequeale.

2.5.3 Discrete Event Simulation

Method

The aim of a Discrete Event Simulation (DES) is to create a model which mimics the behaviour of a real-life system over time. DES is a stochastic technique that allows for the modelling of individual entities through a set of logically separate processes (events). These events can either take place at pre-arranged times, or the event times can be assigned during the simulation. DES techniques process events in continuous time order by using a future events list which maintains a list of all events that are scheduled to take place and the time at which each will occur. In maintaining the future events list and using it to identify the next event to occur, DES models generally run more slowly than Markov models and SD models (Pidd 1992).

Advantages and Disadvantages

The key element that DES offers over SD is the ability to model systems at an individual level (Barton *et al.* 2004). This enables the modeller to capture the variability in donors and patients, while recording every event that occurs and providing the user with a very detailed set of results.

The main advantages (Law and Kelton 2000; Pidd 1992; Robinson 2004) in using discrete event simulation models are that they can be easily understood by health planners (especially with the aid of packages that allow creation of visual models), they can easily incorporate different stages and various factors, making potential models very flexible. DES imposes no implicit assumptions associated

with the methodology and so this adds to their flexibility. DES models can incorporate variability and so lead to a more realistic model. DES models allow for the modelling of very complex scenarios with ease (and does not have to rely on equations being solvable). Once a base model is generated, alternative scenarios are easy to code and so the model can investigate many different scenarios as well as monitoring a number of outputs. DES models can incorporate both statistics information from expert opinions and can reduce the risk of reliance on potentially erroneous or unavailable data. The models can include intangible components and investigation of extremes which could be rare but critical. DES models update the model at times when events occur i.e., implement variable time steps, as to when the model is updated and solved and so can capture all events when they occur and no detail is lost. DES models can also take into account what happened in previous states *very* easily which is important in healthcare modelling.

There are also a few problems that exist in implementing DES models (Brailsford and Hilton 2001; Karnon 2003), which include that the DES model has to be run a large number of times for the results to be statistically significant, especially when the system under consideration is highly variable. It can be difficult to validate the model, especially where the scenario is complex. DES models require a greater time to develop than Markov and SD models. If the DES model is very complex, then it can be hard to isolate and understand what is going on in the model and determine cause and effect relationships. DES

models can take a long time to run; and parameter estimation can be a problem and DES models often require vast amounts of data.

Examples

DES models are widely used in the healthcare context. Common applications include:

- Assessing the cost-effectiveness of interventions such as screening or vaccination (Davies *et al.* 2003; Rauner *et al.* 2003);
- Assessing the benefit of interventions such as screening or vaccination (Brailsford *et al.* 1998; Cooper *et al.* 2002);
- Considering the effects of changes in policy (Pritsker *et al.* 1995; Eldabi *et al.* 2001; Taranto *et al.* 2000; Zenios *et al.* 1999); and
- Projecting future demand for health services (Roderick *et al.* 2004).

Davies and Roderick (1998) and Roderick *et al.* (2004) developed a DES model to help to predict the future demand for renal replacement therapy in England. Their overall findings implied a substantial growth in the renal replacement therapy population to 2010 (with an average annual growth of 4.5-6%) with the greatest increases within the elderly and those with haemodialysis. The model also showed that a steady state would not be obtained for at least another 20 years beyond 2010. The model allows healthcare planners to gain insight into future demand and can aid in future resource planning.

2.5.4 Previous Transplant Matching Studies

Markov Models

Roberts (1992) used Markov models to capture model dying post-liver transplant. He did this by defining probabilities of death for the three stages: 24 hours, 30 days, and long-term after transplantation. The probabilities were based on factors deemed, by a previous study at Deaconess Hospital, to be significant in survival within each of the stages (Roberts *et al.* 1989; cited by Roberts 1992). These factors are presented in Table 2.3 below.

Table 2.3 Significant clinical factors for survival at differing times after transplantation.

Stage	Factors Important for Survival
24 Hours	Creatinine Prior Right Upper Quadrant surgery
30 Days	Creatinine Life support
Long-Term	Re-transplant Crossmatch reaction Infection Bilirubin Malnutrition

Although Roberts (1992) managed to apply Markov techniques to the problem area, he notes that the model has yet to produce usable “answers” to the problem of the optimal timing of liver transplantation in end-stage liver disease because of the lack of adequate data to calibrate the model.

Howard’s model (2001) and the ULAM model (Harper *et al.* 2000) implemented Markov matrices to describe the transitions of patients between UNOS disease statuses and the states of removal from the waiting list, death, and temporarily

inactive/suspended. Since there are few disease states (three in Howard's and four in ULAM), the transitions between the states will occur over substantial lengths of time, hence Markov modelling was ideal for the limited objectives of these studies.

System Dynamics

None of the models in the literature have implemented SD techniques. This is mainly because they are considering the consequences of decisions made on an individual basis - who should be listed for a transplantation; who should be allocated a particular liver; how much better off will someone be if they receive a transplant - and SD is not able to answer these types of question.

Discrete Event Simulation

Of the transplant matching studies; ULAM (Harper *et al.* 2000), the Pittsburgh model (Kreke *et al.* 2002a), LiverSim (Eldabi *et al.* 2001), UKAM (Taranto *et al.* 2000), and Zenios' model (Zenios *et al.* 1999); have all employed DES to model patients progressing through the transplantation systems. DES allows for the monitoring of individual patients and hence is more useful than a SD model for observing the impact of policy changes that are based on characteristics of individual patients. DES also allows for conditional events (unlike Markov models) and the arrival of separate streams of entities, which will be useful in defining when a transplant may take place and the arrival of both patients and donors into the system.

The main limitation of SD which DES overcomes is the granularity of interactions that can be observed. For this current model we wish to consider interactions between donors and patients and consider outcomes of individual patients. SD only considers the general flows of patients and donors and not the individuals within the system. SD also cannot allow for matching between donors and patients. DES can consider the general flows, the individual interactions, and the criteria by which to match a donated liver to a patient and hence is more useful in the current context.

Brailsford and Hilton (2001) and Barton *et al.* (2004) acknowledge that the decision as to which modelling technique should be adopted depends on the purpose of the model (i.e., what sort of questions the model needs to answer). SD focuses more on the overall behaviour of certain aspects of a system, while DES follows individual patients through the system. Hence SD models have been used to examine strategic decisions, whereas DES models have traditionally been applied at tactical, operational levels. DES also overcomes the main limitations of Markov Models, as it can easily incorporate both non-constant hazards over time and can base outcomes on all prior events.

2.6 Research Objectives and Questions

Chapters 1 and 2 have identified the key motivations of this thesis. The aim of this research is to study the UK liver transplantation system, creating a model based on available clinical and social data with which to explore the impact of

different assessment and allocation decisions on various equity and utility measures.

It has been illustrated in this chapter how little has been done to explore UK liver transplantation allocation rules and to investigate new policies. No attempt has been made to develop a model for the UK which brings together detailed survival analysis across all transplantable liver diseases and explores adaptive methodologies by which to generate policies. Some studies have been carried out in the US, but these have concentrated on identifying detailed natural histories. The UK system is different in that patients are only placed onto the waiting list once their life expectancy falls under a particular level – one year. This means that the modelling of disease histories is less important. The model which has been created and described in this thesis considers many of the shortfalls in previous models and attempts to develop a model which is suited to the UK liver transplant system.

The specific research objectives and questions that this work aims to answer, are identified next (in Sections 2.6.1 and 2.6.2, respectively).

2.6.1 Research Objectives

The research objectives for this work (covering the three aspects, identified at the end of Section 2.2.3) are:

- (1) The identification of suitable measures to enable comparison between policies;

- (2) The identification of a technique by which to estimate the time a patient will stay in a particular state (events and survival); and
- (3) The identification of a methodology by which to model patient progression through the system.

2.6.2 Research Questions

The research questions this work aims to answer, are:

Suitable Measures to Enable Comparison Between Policies

‘Can we get a better understanding of whether alternative allocation policies can improve both equity and utility, simultaneously?’

‘Does the complexity of the allocation rules affect the equity and utility outcomes?’

‘Do the policies which improve equity and/or utility, continue to do so as demand and supply changes?’

Estimating Events and Survival

‘Can we find a parametric distribution using statistical techniques that can be sampled from within a DES?’

Patient Progression

‘Can a simulation answer questions in the UK context about equity and utility within the transplant allocation and assessment process?’

2.7 Summary

This chapter began by summarising the literature on previous transplant matching studies. Many of the studies are from the USA and although there are characteristics in common, these are not directly applicable to the UK transplantation systems due to inherent differences in how the two systems operate. Most of the models are not suitable for evaluating different policies as they do not capture all the detail that is required. In order to do this it is necessary to:

- Model outcomes in terms of both equity and utility;
- Model all patient groups;
- Identify the likely trends in future demand and supply; and
- Include the assessment phase within the model.

From the literature search three key areas, which form the research objectives, were identified as important aspects for consideration when developing a representative model of the liver transplant matching problem:

- (1) The identification of suitable measures to enable comparison between policies;

- (2) The identification of a technique by which to estimate the time a patient will stay in a particular state (events and survival); and
- (3) The identification of a methodology by which to model patient progression through the system.

The previous transplant matching models have all captured these three elements to varying extents. However, no single project has looked at all three in the context of the UK Liver Transplant System.

A review of OR and Statistical techniques commonly employed in healthcare applications and which enable the modelling the three key aspects identified is presented. The review includes a discussion of equity and utility measures, Survival and Competing Risks models, Markov models, System Dynamics and Discrete Event Simulation. A summary of the advantages and disadvantages of using these techniques is given with identification of how the previous transplant studies have used them.

Chapter 3

Methodology

3.1 Introduction

This chapter sets out the methodology required to develop the DES model (Hepatica) for investigation into the dynamics of the UK liver transplantation system, under various assessment and allocation policies. A list of experimental factors and key response measures is given, with a detailed outline of the structure of Hepatica. The chapter ends by summarising the experimental design to consider various changes to the current assessment and allocation policies.

3.2 Objectives and Choice of Models

3.2.1 Problem Situation

It was identified in Chapter 1 (Sections 1.2.5-1.2.6) that the number of patients requiring liver transplantation exceeds the number of livers donated and that the trends in demand and supply suggest the gap will increase in the future. As a result, it is important to utilise the donated livers in a way which generates the best overall patient outcomes, while ensuring that all patients on the waiting list have a fair chance of receiving a transplant.

Section 1.3.3 established the main parts of the liver transplantation system at which policies can be adjusted to influence the outcomes of the system:

- (1) The Assessment Phase (where a patient's suitability for transplant is assessed); and
- (2) The Allocation Phase (when donated livers are allocated to one of the patients on the waiting list).

3.2.2 Modelling Objectives

Hepatica seeks to overcome many of the limitations identified in the previous models, in particular:

- Estimates of future demand and supply (which are detailed in Section 3.3.1 and 3.3.2);
- Changes to criteria implemented in the assessment phase (as outlined in Section 3.3.3);
- All liver diseases that can be treated by a liver transplant;
- Super urgent patients. This is a significant inclusion as they receive priority for liver transplantation;
- Survival times to be based on key patient, donor and transplant attributes (as outlined in Section 3.7.2); and
- Factors in the system itself which explicitly influence the decision as to who is allocated a donor (as described in Section 1.3.5), for example, the location of the patient and the donor.

The modelling objectives have been discussed in Section 2.6 and are summarised below:

- The identification of suitable measures to enable comparison between policies;
- The identification of a technique by which to estimate the time a patient will stay in a particular state (events and survival); and
- The identification of a methodology by which to model patient progression through the system.

3.2.3 Choice of Model

Chapter 2 identified three key areas which require consideration when developing a model of the UK liver transplantation system (Section 2.2.3).

These are, to identify:

- (1) Suitable measures for comparison between policies;
- (2) A technique by which to estimate the time a patient remains in a particular state; and
- (3) A methodology by which to model patient progression through the system.

The solutions identified are outlined below.

(1) Outcome Measures

The overall responses considered in Hepatica fall into the two groups of equity and utility measures. These were chosen to enable an assessment to be made about how fair a particular policy is in allocating liver transplants across various

patient groups, and of how effectively a policy uses the donated livers. The actual measures considered are outlined in detail in Section 3.4.

(2) Estimating the Time Spent in a Particular State

Survival models or competing risks models are appropriate for capturing the times that patients spend in particular states, since the datasets used to develop the models will be censored. Survival analysis and competing risks models allow for parametric distributions to be generated, which will allow for the development of distributions that can be easily sampled from, and used within the DES model.

(3) Modelling of Patient Progression

Discrete Event Simulation was chosen for the modelling of patient progression through the liver transplantation system since it takes into account a number of patient attributes, and allows for patient and donor-level modelling.

The DES model will only consider adult patients (those aged 17 and over), as the adult patients make up most of the waiting list, and the liver diseases that adults suffer from differ considerably from those which children experience.

Hepatica is programmed in Witness as the software provided all of the functionality required within the model.

Terminology

Within the rest of this thesis the term *scenarios* will be used to denote the situations considered by each run of the DES model. Each scenario will therefore consist of a set of experimental factors (i.e., current and future demand, current and future supply, assessment rules, and allocation rules), which are explained in more detail in Section 3.3.

3.3 Experimental Factors/Inputs

The experimental factors are the elements of the model that can be adjusted when considering various scenarios and within the scope of Hepatica they fall under the four headings:

- (1) Demand Factors - Adult Patients requiring Liver Transplants;
- (2) Supply Factors - Liver Donations made to Adult Patients;
- (3) Assessment Rule Factors - Patient Eligibility for Receiving a Liver Transplant; and
- (4) Allocation Rule Factors - Patient Priority for Transplant and Donor to Patient Matching.

The various factors to be investigated are outlined in detail in the remainder of this section.

3.3.1 Demand Factors - Adult Patients requiring Liver

Transplants

The baseline for the experimental demand factors is the number of patients observed to have joined the liver transplant waiting list from 1 January 1999 to 31 December 2002 (UK Transplant 2004e). Additional factors have been created following work performed by Roderick *et al.* (2004) (detailed in Section 1.2.6), which predicted increases in the number of sufferers from Alcoholic Liver Disease, Non-Alcoholic Fatty Liver Disease (NAFLD) and Hepatitis C.

For Alcoholic Liver Disease the actual experimental factors used are based on the alcohol consumption trends for the years 1974 to 2004 (Institute of Alcohol Studies 2006). Similarly, increases in NAFLD are assumed to follow trends in obesity (Zaninotto *et al.* 2006). For Hepatitis C, the findings from Roderick *et al.* (2004), are taken to define the three different trends: 2.5-fold, 3-fold, and 4-fold increase in the number of Hepatitis C sufferers emerging for liver transplantation.

Four different demand factors are considered, the base factor D1 assumes a constant number of adult patients falling ill within each of the disease groupings, based on the average number of patients joining the waiting list each year between 1999 and 2002. The other factors (D2, D3 and D4) assume an increase in demand over time. Factors D2, D3, and D4 differ only by the rate of patients requiring liver transplants due to Hepatitis C. All the trends defined within the

factors fit proportionally with the cited references and are illustrated in Figure 3.1 and Table 3.1, below.

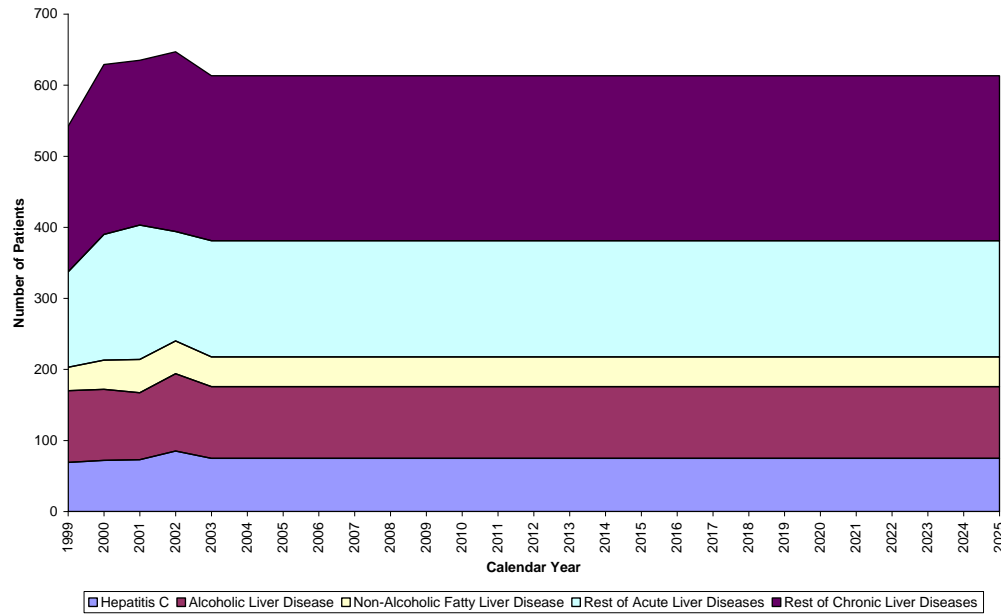


Figure 3.1 Constant Demand Factor (D1).

Table 3.1 Demand Factors to be Investigated.

	Constant Demand (D1)	Demand Increasing (D2) 122 extra over 4 years	Demand Increasing (D3) 193 extra over 4 years	Demand Increasing (D4) 146 extra over 4 years
Hepatitis C	75	71	142	95
Alcoholic Liver Disease	101	25	25	25
Non Alcoholic Fatty Liver Disease	42	26	26	26

3.3.2 Supply Factors - Liver Donations made to Adult Patients

Figure 3.2 shows the number of liver transplants which have been performed on adult patients over the period 1 April 1999 to 31 March 2006⁷. After increasing by 17% between the years 2000/01 and 2003/04, the number of transplants have fallen by the same margin between the years 2003/04 and 2005/06.

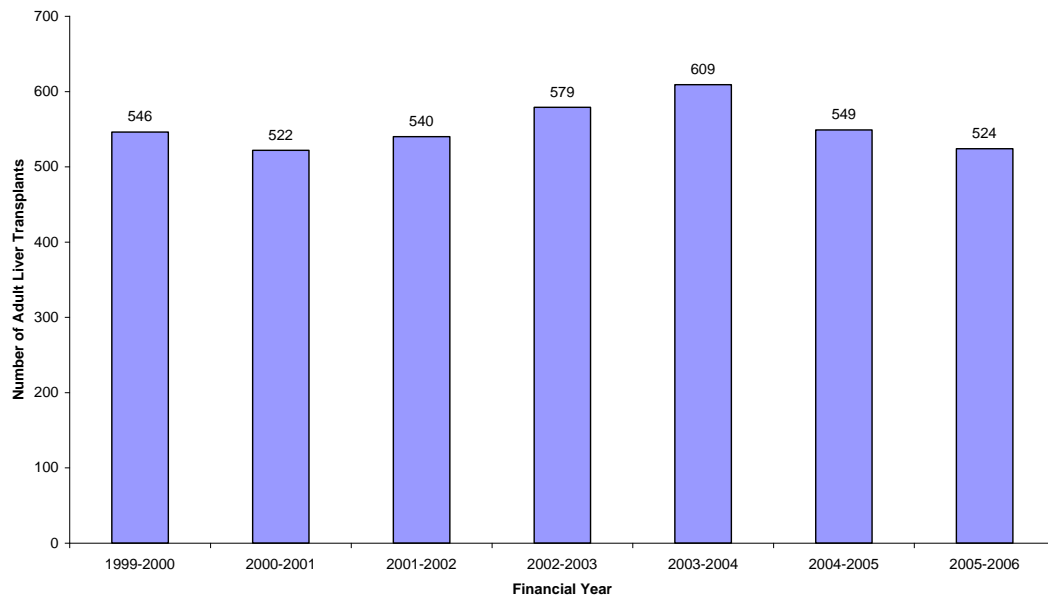


Figure 3.2 The number of adult (patients aged 17 years and above) liver transplants to take place in the UK, from 1 April 1999 to 31 March 2006 (UK Transplant 2001b; 2003c; 2004f; 2005c; 2006).

The supply factors created consider possible changes to the number of adult transplants performed over the course of the next 20 years. The differences between these factors are discussed below and are illustrated in Figure 3.3.

⁷ Please note that the data available for creating the demand factors (in Section 3.3.1) was based on calendar years, while for the supply factors the data used is based on financial years. Although this is not ideal, due to donation rates remaining more-or-less constant over the years, the overall results will not/should not be affected greatly.

Constant Supply (S1)

From Figure 3.2 it can be seen the number of adult liver transplants carried out fluctuates around an average of 553. The first factor (S1) assumes that this number will not vary significantly in the future and is based on a constant number of liver transplants being available to adults each year. Factor S1 generates a possible 565 adult transplants a year, based on an average of the last four years (i.e., from 2002/03 to 2005/06).

Declining Supply (S2)

From Figure 3.2 it can be see that the number of adult liver transplants taking place over the most recent 3 years, (2003/04 to 2005/06), has been declining. Therefore, factor (S2) considers the effect of a declining number of transplants being available. The decline is assumed to continue at the average rate for these three years, which is 43 fewer donations per year.

Increasing Supply, over 10 years (S3) and over 20 years (S4)

Two factors (S3 and S4) examine the hypothetical effect of increasing the number of livers donated (which could result from successful awareness campaigns (Section 1.2.6) or as a result from a change in legislation to an Opt-Out policy (Section 1.5.1)). Factors S3 and S4 consider situations where the donation of livers for use in adult transplants increases to the same levels as Spain (as outlined in Section 1.5.1), over the course of the next 10 years (S3) or 20 years (S4). An increase in donations rates of this magnitude may not be

likely, but it is of interest to explore the potential benefits obtained from the number of donations increasing to these levels.

The factors assume a pro rata increase for the number of liver donations available. This may underestimate the effect of an increasing donation rate, since children receive priority within the current system (Section 1.3.5) and so most children in need of a liver transplant, already receive a transplant.

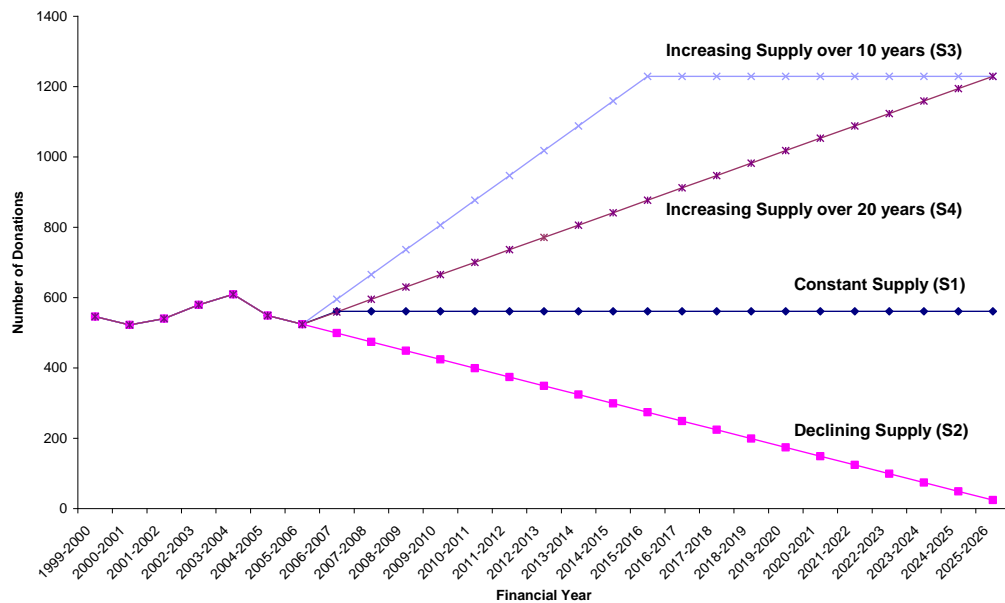


Figure 3.3 Supply Factors to be Investigated.

3.3.3 Assessment Rule Factors - Patient Eligibility for Receiving a Liver Transplant

Currently, patient suitability for transplantation is judged on strict definitions of pre- and post-transplant life expectancies, as outlined in Section 1.3.4. The original intention was to incorporate the assessment process into the model.

This would allow for different assessment criteria to be tested, affecting the number of patients joining the waiting list and the severity of their disease. However, due to data limitations (as presented in Section 4.3.3) this has not been possible. Instead, the potential impacts of changes to the assessment criteria have been mimicked by making changes to the prognoses of patients who arrive on the waiting list (within the revised model, Section 4.3.3). Changes to the assessment criteria need to be investigated since if the supply falls further relative to demand, the assessment rules will need to be made more restrictive in order to keep the size of the waiting list as a manageable level.

To achieve this, three assessment rule factors have been created where the prognoses of patients are varied, but in each case the same number of patients is added to the waiting list each year.

- For the base factor (A1), patients have the same prognosis as observed for UKT patients between 1999-2002.
- The second factor (A2) represents the situation where assessment rule A (current life expectancy) is made more restrictive, and in order to be eligible for transplantation, patients have to be at a later stage of their disease than is currently the case.
- The third factor (A3) represents the situation where assessment rule A (current life expectancy) is made more restrictive, and in order to be eligible for transplantation patients have to be at an earlier stage of their disease than is currently the case.

Factors A2 and A3 will be constructed by either multiplying all the generated Death/Removal times (Equations (4.3) and (4.4) Section 4.4.2) by 0.9 (for poorer prognosis) or multiplying by 1.1 (for better prognosis).

3.3.4 Allocation Rule Factors - Patient Priority for Transplant and Donor to Patient Matching

To determine feasible allocation rule factors (i.e., those which would be realistic to implement) some work was performed to identify the components which could be used in determining possible alternative factors, and these are listed in Table 3.2.

Table 3.2 Allocation Rule Components.

Factor	Priority To
Matching by donor and patient blood groups	Identical blood groups. ABO-compatible blood groups (Appendix B). Incompatible blood groups (Appendix B).
Matching by patient and donor centre	Local patients. National patients. Nationally to super urgent patients and locally to routine patients.
Priority by patient liver transplant number	Patients waiting for their first transplant. Patients waiting for their successive transplant.
Priority by patient age	Youngest patient. Oldest patient.
Priority by the amount of time a patient has been waiting for a liver transplant	Patient with the shortest waiting times. Patient with the longest waiting times.
Matching donor's weight to patient's weight	Donor and patient weights are the closest.
Allocation based on the expected survival benefit (i.e., Utility)*	Patients who have worst pre-transplant prognosis. Patients who will gain most survival benefit between pre-transplant and post-transplant prognoses. Patients who with the best post-transplant prognosis.
Allocation based on equity between patient groups	A policy which is based on improving the equity for patient groups that have received fewer transplants in proportion to the rest of the patient population, under all other allocation rules. Allocate always with the aim to being both compatible and equitable across this attribute.

** In practice, a policy which considers survival times would not be feasible for implementation since accurate estimates of survival would not be attainable, however, the results from investigating this type of policy will give us insight into what the best possible utility outcomes.*

The allocation rule factors considered at the outset are listed in Table 3.3. After observing the results of scenarios which incorporated these factors, additional allocation rule factors were formed by running two or more factors in parallel. The process by which extra factors were identified is explained within the

experimental design section of this chapter (Section 3.8). This section outlines the alternative allocation rules to be investigated, as defined at the outset.

Table 3.3 Allocation Rule Factors to be investigated (full details in Appendix F).

Factor Name	Allocation Rules
L1	<i>Old base allocation rules (Allocation rules in place up to July 2006, modelled for validation purposes.)</i>
L2	<i>Current base allocation rules (Allocation rules in place since July 2006, modelled to create a baseline which to compare all other models to.)</i>
L3	<i>Priority given to patients with any compatible blood group to the donor</i>
L4	<i>Priority given to patients with an identical blood group to the donor</i>
L5	<i>Priority given to patients in the same centre where the donated liver is retrieved</i>
L6	<i>No priority given to patients from the retrieving centre</i>
L7	<i>Priority given to patients registered for their first transplant</i>
L8	<i>Priority given to patients registered for a successive transplant</i>
L9	<i>Priority given to younger patients</i>
L10	<i>Priority given to older patients</i>
L11	<i>Priority given to patients who have been waiting the shortest time</i>
L12	<i>Priority given to patients who have been waiting the longest time</i>
L13	<i>Priority given to patients where the absolute difference between donor and patient weight is minimised</i>
L14	<i>Priority given to patients with the soonest death or removal time (i.e., worst pre-transplant prognosis)</i>
L15	<i>Priority given to patients with the best prognosis post transplant</i>
L16	<i>Priority given to patients with best prognosis compared to expected prognosis without a transplant</i>
L17	<i>An adaptive policy which attempts to make allocation decisions through keeping track of equity measures, for groups not fairly transplanted across, within the other allocation policies</i>

The allocation rules were changed in July 2006 based on findings summarised in a Liver Advisory Group report (Hamilton and O'Neill 2006). The study compared patients within the two time periods 2001/02 and 2003/04 and found a significant increase in the median waiting time to transplant for blood group O patients between the two years. They also found that in 2003/04, blood group O patients waited significantly longer to receive a transplant than blood group A and B patients; with median waiting times 132 days compared with 73 days and

41 days respectively. These differences had not been found within the 2001/02 cohort of patients. Also, a smaller proportion of blood group O patients were transplanted in 2003/04 and a larger proportion had died after one year of registration onto the waiting list. Again, these differences were not present in the 2001/02 data. These findings resulted in the allocation rules being amended to allow blood group O donors to be allocated to blood group O patients before blood group B patients.

The allocation rule that is currently in place (factor L2 below) gives priority to patients with a blood group which is compatible to the donor's, to super urgent patients and to patients from the centre associated with the retrieval area of the donor. The allocation rule also imposes the restriction that livers donated from donors with blood group O must go to a patient with blood group O (if there is such a patient on the waiting list) before any other compatible patient. Factor L1 represents the policy that was in place during 1999-2002 (when data for this project were collected) and this factor is used in validating the initial DES model (Chapter 5). Factor L1 is similar to L2 except that in L1, patients with blood group O or B both received priority for livers donated from blood group O donors. Factor L2 will be used when generating the base case scenario, which will be compared with the alternative policies detailed below.

The exact priority orderings for each of the allocation factors listed in Table 3.3 are presented in Appendix F. All of the factors L3-L17 are designed to identify the effects of changing the priority orderings for transplantation, on utility and

equity. Factors are designed to apply stringent (e.g., L4 and L5) and more relaxed (e.g., L3 and L6) rules compared to the current allocation policy (L2). They also consider patient characteristics, such as the number of previous transplants a patient has had (L7 and L8), a patient's age (L9 and L10), the time the patient has been waiting (L11 and L12), and patient weight (L13). Factors L14-L16 use survival and competing risks models to predict pre-transplant and post-transplant death times for all patients and then allocate the liver transplants to patients based on giving priority to the patient who:

- Will gain the most LYs from receiving the transplant (based on the competing risks models' prediction, Equations (4.3) and (4.4) Section 4.4.2) – L14;
- Will gain the most LYs from the transplant (based on the survival model prediction, Equation (4.6) Section 4.5.2) – L15; and
- Has the best prognosis with a transplant compared to their expected prognosis without a transplant – L16.

L14-L16 will seek to maximise the utility measures. L17 on the other hand will be devised to create greater equity across the group for which policies represented in factors L2-L16 are most unfair.

3.4 Responses/Outputs

As already discussed (Section 3.2.2), one of the objectives for modelling is to compare various assessment and allocation policies to help identify alternative policies which:

- (1) Provide the most equity (encourage fairness) between various patient groups within the pool of ESLD sufferers; and
- (2) Allocate the donated livers in the most effective way (i.e., yielding the best overall patient outcomes).

No single measure exists to assess both the effectiveness and fairness of differing policies. In fact, to identify the overall fairness and effectiveness of the liver transplantation system, equity and utility measures must be considered at various stages within the transplantation process (as explained in Sections 2.3.1 and 2.3.2).

In the UK, patients are listed on the WL if they meet the requirements for transplantation and are estimated to have a more than 50% probability of survival at 5 years after transplantation with a quality of life acceptable to the patient (as explained in Section 1.3.4). This approach restricts transplantation to those who are most likely to benefit from the procedure, and the emphasis of utility rather than equity has ethical issues (Neuberger c.2004).

The response measures recorded will determine whether the modelling objectives have been met, as well as, by how much they fell short, if the modelling objectives were not met.

As mentioned in Section 2.3.4, ULAM (Pritsker *et al.* 1996) provides the most comprehensive list of equity and utility measures. Table 3.4 below summarises

the equity and utility measures which Hepatica uses and indicates where the measures are present in ULAM.

*Table 3.4 Output Measures for Hepatica. * are measures which are present in the output module of ULAM (Pritsker et al. 1996).*

Stage	Type of Measure	Measure	Statistical Test/ Observation to be made
Referral to liver unit (by GP)	Equity	Probability of being referred to a liver unit	Similar percentages across groups
		Probability of dying before hospital referral appointment	Similar percentages across groups
	Utility	Probability of dying before referral	Minimum across policies
Outcomes from referral (referral → assessment and referral → join the waiting list)	Equity	Probability of joining the waiting list	Similar percentages across groups
		Probability of dying in assessment stage/previous to the assessment stage	Similar percentages across groups
	Utility	Probability of dying before joining the waiting list	Minimum across policies
Outcomes from the waiting list (WL → transplant, WL → death and WL → removal) and post transplant outcomes	Equity	*Probability of receiving a transplant (once on WL)	Similar percentages across groups
		*Probability of dying or being removed from the waiting list	Similar percentages across groups
		*Waiting list size through time	Similar size across time
		*Probability of dying or suffering graft failure post transplant	Similar percentages across groups
		*Probability of being re-listed post transplant	Similar percentages across groups
		*Probability of experiencing death or graft failure post transplant	Similar percentages across groups
	Utility	*Size of the end waiting list	Minimise the size
		*Gain in Life Years (LYs) per transplant	Maximum across policies
		Life Years in the System per patient	Maximum across policies
		*Number of wasted livers	Minimise
		*Percentage patients re-listed (within 1 year)	Minimise percentages
		*Probability of experiencing death or graft failure post transplant (within 1 year)	Maximum across policies
		*Probability of dying or being removed from the waiting list	Minimum across policies

3.4.1 Equity Measures within Hepatica

Equity measures convey the overall fairness of the liver allocating system and as identified in Section 2.3.1 equity measures need to be considered at all stages within the liver transplantation system; from a person falling ill with End Stage Liver Disease to their eventual death. The previous liver transplant matching studies, including the ULAM, only consider equity at the stage of the allocating of livers and therefore do not capture the overall extent to which the system is equitable. Other studies, including LiverSim do not consider how equitable their policies are. In the US, this issue is less of a concern since everyone with ESLD can be listed for transplantation.

In the UK, equity of access to liver transplantation by the geographical location of the patient, must also be considered at the stage of referral to the liver unit, then progression to the waiting list, and the eventual outcome. This is because there are only seven liver units and none of these are located in South West England (as depicted in Appendix C), so there could potentially be an unrepresentative number of patients being referred from this area. Appendix G reports on analysis performed on the probability of being assessed as suitable to join the waiting list, based on where the patient was resident, within a particular liver transplant unit. Appendix G also reports on some work which Roderick performed in evaluating the probability of obtaining a transplant, once on the waiting list, by patient residence. The main limitation of both analyses is that they assume that patient demographics within all parts of the UK are similar.

Both analyses however do report that no patient seemed to have an advantage in obtaining a liver transplant, based on where they lived.

The main equity output measures that Hepatica considers are listed in Table 3.4. The table also describes the statistical and observational techniques which were employed in identifying the policies which are equitable and the policy which is the most effective. The equity measures are recorded by the groupings: age, location, blood type, transplant number, and disease type. ULAM considered additional measures which included the local use of organs and the impact of this on organ donation rates within the region, policy impacts on geographic areas, costs of transplantation, transitions between medical statuses, the distances livers travel, and the time different patient groups spend waiting for a liver transplant. These factors are not considered explicitly within Hepatica for the following reasons:

- This study is not focusing on factors connected to organ donation rates;
- Currently there is evidence to suggest that equity exists amongst different geographic areas within the UK (Appendix G) and there is no reason to suppose this will change;
- The major costs resulting from transplantation will remain the same (we will still have the same number of transplants take place);
- Transitions between medical statuses will be less likely than within the US system, as patients in the UK are placed on the WL only if they are expected to die within a year; and

- The time different patient groups spend waiting for a transplant only begins to matter:

- If patients in particular groups miss out on transplantation, or
- If a delay in certain groups receiving a transplant affects the post transplant outcome which they experience.

These two aspects are already being monitored within the measures:

- The percentage of deaths and removals from the waiting list, and
- The proportion of re-lists and death/graft failure events post transplant.

Table 3.4 lists equity measures that will determine achievement or non achievement of the modelling objectives. In terms of equity we are seeking to improve the fairness of the allocation of donated livers, or the progression of patients from one state to another, by patient group. To measure this aspect we can observe the actual number of patients experiencing particular events and compare this to the expected number to experience the events across the patient groups (i.e., total patients in the group multiplied by the overall percentage of patients to experience that particular event). If we sum up the absolute differences across the groups, we obtain an indication of how “unfair” the policy is across the groups for a particular event. Ideally, we wish this sum to be as small as possible, for the policy to be fair. If we calculate this statistic for the base scenario then we can determine if the alternative policies meet our objective for modelling (identifying a policy which improves equity), or fails to do so.

Chapter 6 Section 6.2.2 presents equity values of the current system, over the years 1999 to 2002, as calculated using the UK Transplant data set (UK Transplant 2004e).

3.4.2 Utility Measures within Hepatica

Utility measures convey the overall utilisation of the donated livers and how effective by different parts of the system operate. As explained in Section 2.3.2, utility measures attempt to evaluate the benefit gained through implementing a certain policy. The previous liver transplant matching models have concentrated on: (1) identifying the gains in survival due to liver transplantation, (2) the cost-effectiveness of liver transplantation, and (3) more recently some modellers have started to consider the effect of liver transplantation on a patient's QoL (Kerke *et al.* 20002b).

The main utility output measures that Hepatica considers are listed in Table 3.4. These measures will be considered for a particular policy, and not separately by patient groups, as we wish to identify the overall ability of a policy to effectively use the donated livers. The main utility aspects that are considered in previous liver transplant matching models, and not within Hepatica, are:

- The costs involved in liver transplantation, (since there is currently no alternative to liver transplantation, and either a patient is transplanted or they soon die, it is more important to consider patient survival);
- The QALYs gained under various policies are important. However, as patients who are placed on the waiting list are so near death it is more

important to identify the impact of a policy on overall survival (i.e., Life Years gained per transplant). QoL data has a key limitation, in that it is subjective and different groups of patients may view the *same* QoL, differently (Davies *et al.* 2003); and

- In many medical systems the average waiting time would also provide us with a utility measure. However, this measure is not relevant in this situation as the average waiting times will just resemble the average times between successive donated livers, within the observation period. Thus, this measure becomes meaningless in this context, in terms of representing how effectively a particular policy is in providing patients with liver transplant on a timely basis.

To identify whether a new policy achieves the objectives for modelling the utility measures from the new policy as outlined in Table 3.4 are compared (as indicated in column 4) to the values obtained from analysis of the base scenario.

Previous liver transplant matching studies which consider the total number of LYs gained under a particular policy, use the *Total Gain in Life Years per Transplant* calculation depicted in Equation (3.1). Hepatica also evaluates this measure in addition to the *Total Life Years in the System per Patient*, as depicted in Equation (3.2). This latter measure attempts to obtain an idea of how well a policy picks patients for transplantation, with the aim of maximising the total number of LYs of the whole patient cohort. This will give more insight into how patients might be chosen to utilise donated livers “optimally”.

Total Gain in Life Years per Transplant:

$$\frac{\sum_{i \in I} \{E_i(\text{Death time if transplanted}) - E_i(\text{Death time if not transplanted})\}}{N} \quad (3.1)$$

where I = the set of all the patient transplants that took place,

N = the total number of transplants to take place (i.e., count of I),

$E_i(\text{Death time if transplanted})$ = the time a patient is predicted to die, once they receive a transplant,

$E_i(\text{Death time if not transplanted})$ = the time a patient is predicted to die, once they have joined the waiting list.

Total Life Years in the System per Patient:

$$\frac{\sum_{j \in J} \{E_j(\text{Final Death time}) - E_j(\text{Death time on first registration})\}}{M} \quad (3.2)$$

where J = the set of all patients who joined the waiting list,

M = the total number of patients to join the waiting list (i.e., count of J),

$E_j(\text{Final Death time day})$ = the time at which a patient eventually dies (if they receive no transplant then the time they are predicted to die, once they have joined the waiting list; if they receive a transplant then the time they are predicted to die post transplant),

$E_j(\text{Death time on first registration})$ = the time a patient is predicted to die, once they have joined the waiting list for the first time, within the observation period.

3.4.3 Overall Scoring of Values

Attempting to improve the utility measures of the system may sometimes have an adverse effect on the equity measures. For example, the overall potential gain in LYs will be dependent on the age of the patient, and so trying to maximise this measure may lead to the elderly, who will generally be expected to have their lives extended by fewer years, not being treated at all. Conversely, a policy which aims to maximise allocation fairness (improve equity within the system) will allocate to all age groups at the expense of maximising utility measures. Another important factor for which a similar effect may arise is disease group, where some disease groupings have poorer prognoses post transplant (e.g., patients with diseases that commonly recur as discussed in Section 1.4.2). Hence, the “best” policy will not simultaneously maximise utility and equity and so the measures will need to be prioritised into an order of relative importance. This issue resembles one of the main trade-offs and ethical issues within organ allocation (as discussed in Section 2.3.3).

As some policies will create equity between patient groups and may not maximise the utility of the donated liver organ, and vice versa, it is important to define how to balance measures observed in Hepatica. The main objective of our modelling is to identify policies which improve upon the equity and utility outputs of the base scenario, therefore, each of the equity and utility measures produced by various scenarios, were compared to the measures observed from the base scenario. It was then decided whether the values returned by a particular scenario were either: (1) better than (i.e., an improvement), (2) the

same as (i.e., no improvement), or (3) worse than (i.e., the new policy results in a negative affect on the measure) those returned by the base scenario. Most values were considered the same if they fell into a band of 2.5% greater or less than the value observed as the base scenario value. The only exceptions were the utility measures which evaluated the total life years gained per transplant and the total life years per patient in the system; for these measures we used the 95% confidence intervals to determine whether the scenario is (1) better than, (2) the same as, or (3) worse than the base scenario in extending the life years for the patients. If the CI overlapped then it was assumed that the new scenario could not be shown to have changed the number of LYs over the base scenario, i.e., was not any better or worse than the original scenario. If the CI of the scenario was outside of the CI of the base scenario then the policy was either assumed to be better or worse than the base scenario, depending on which CI covered higher values. Each value was then given 1 point, 0 points, or -1 points, corresponding to whether the outcomes were better than, the same as, or worse than the base scenario outcomes. These values were then weighted and summed together (as explained in Section 6.2.2), to rank the policies in terms of improvement.

The weighted sum representing the improvement in equity was then plotted against the weighted sum representing the improvement in utility. This graph was then analysed to identify the policies that improve equity and utility (and the results are reported in Chapter 6).

3.5 Simulation Model Outline

The idea behind this thesis is to model patient progression through the liver transplantation system. The intention is to find the most appropriate match between a donated liver and one of the patients on the waiting list, by examining their (individual) characteristics. We also wish to know the outcomes, with and without transplantation, that are experienced by each of the patients so that we may compare various matching policies and assess the overall utility of various policies (as discussed in Section 3.4.2).

3.5.1 DES Model Structure

Figure 3.4 below details the simulation model to be developed (Hepatica). The diagram captures the stages that a patient passes through from initial referral. It includes the patient flows after referral based on the stages outlined in Figure 1.4 (Section 1.3.3) and extended to include post transplant outcomes. Hepatica includes: (1) the referral stage, and (2) the assessment stage, which are reconsidered in Chapter 4 when the sub-models are created.

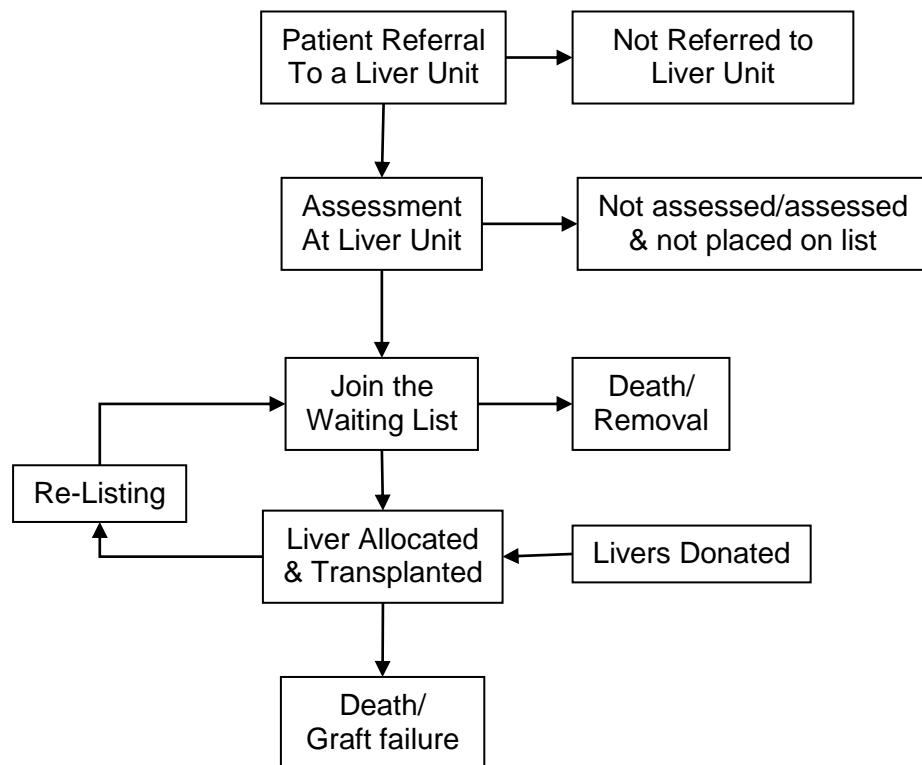


Figure 3.4 A flow diagram to depict the process once a patient is diagnosed with ESLD.

The focus of Hepatica has been to incorporate the key stages of the process where the observed responses (as outlined in Section 3.4) of a particular policy need to be evaluated. This section outlines the sub-models developed to enable predictions at the various stages within Hepatica. The appropriate modelling techniques for each of the transitions and flows are explained in Section 3.6. Tables 3.5 to 3.7 summarise the scope of the model and the level of detail to be incorporated.

Table 3.5 Model Scope - Components included.

Component	Justification
Patients Arrivals (ill will ESLD)	Determines the demand for transplantation and the patient flow rates through the transplantation process
Donors Arrivals	Determines when a transplant may take place
Patient Referral to Liver Unit	A patient must be referred to a liver unit, as an initially step to obtaining a liver transplant. Determines patient flow through the system
Assessment Phase	A patient needs to pass the assessment phase (i.e., to be judged suitable for transplant) in order to be placed onto the WL and obtain a transplant. Determines patient flow through the system
Waiting List/Queue for Transplant	A transplant is allocated to patients that are on the liver transplant WL. Determines patient flow through the system
Allocation	The process by which it is decided who will receive a liver transplant. Determines patient flow through the system
Re-list post transplant	Patients that also require transplant. Determines patient flow through the system
Death/Removal from WL	If a patient is removed or dies from the WL, then they are no longer waiting for a transplant. Determines patient flow through the system
Death/Graft Failure from transplant	Overall outcome. We know that these patients will no longer require another transplant. Determines patient flow through the system

Table 3.6 Model Scope - Components excluded.

Component	Justification
Number of Liver Transplant Surgeons	Not relevant for the overall outcomes that are being evaluated
Number of Liver Transplant Units	Not relevant for the overall outcomes that are being evaluated
Government Campaigns	Have not affected donations significantly. But add to “What-If” scenarios by changing the supply
Opt-In/Opt-Out	Not likely to change, however, added to “What-If” scenarios by changing the supply

Table 3.7 Components - Level of Detail Included in Hepatica

Component	Detail	Comment
Patients	Patient inter-arrivals	Sets the patient flow into the system. Modelled as a distribution
	Patient attributes	Helps to determine eventual outcomes. Modelled as several distributions
Donors	Donor inter-arrivals	Determines when a transplant may take places. Modelled as a distribution
	Donor attributes	Helps to determine eventual outcomes. Modelled as several distributions
Referral Phase	Process	Determines who is put forward for transplant. Represented by a set of rules
Assessment Phase	Process	Determines who is put forward for transplant. Represented by a set of rules
Waiting list/Queue for Transplant	Queuing	Required to determine waiting times and determine the number and type of patients waiting for a transplant at any one point in time
Allocation	Process	Determines who is allocated a transplant. Represented by a set of rules
Re-list post transplant	Process	Determines who requires another transplant. Represented by a set of rules
Death or removal from waiting list	Times	Determines the time at which a patient will die or be removed from the WL i.e., no longer requiring a transplant. Modelled as several distributions
Death or graft failure from transplant	Times	Determines the time at which a patient will die or suffer from graft failure and hence no longer require a liver transplantation. Modelled as several distributions

The key phases of the model as depicted in Figure 3.4, are:

- (1) **Arrivals** (patient referrals to a liver unit and liver organs donated);
- (2) **Assessment Phase** (the process by which it is determined whether a patient is suitable for transplant and hence whether they should join the waiting list or not); and
- (3) **Allocation/Transplant Phase** (the process by which a donated liver is allocated to a patient so that the patient may have a transplant);

- (4) **Outcomes** (these are death or removal from the waiting list; death or graft failure or re-listing once transplanted).

To be able to capture these key phases, Hepatica must include the following components:

- (1) Patient Generation and Patient Attribute Assignment;
- (2) Donor Generation and Donor Attribute Assignment;
- (3) Transplant Assessment Rules;
- (4) Survival Time Generation {(1) the time from joining the waiting list to dying or being removed, (2) the time from receiving a transplant to dying or suffering from graft failure, (3) the time from receiving a transplant to being re-listed for another liver transplant operation};
- (5) Maintain a list of candidates on the waiting list; and
- (6) Transplant Allocation Rules.

Sub-models that capture these aspects are discussed in the next section.

3.6 Techniques used for Developing the Sub-Models

3.6.1 Arrivals and Attributes Generation

Patient and Donor Generation and Attribute Assignments

Analysis was performed for both patient and donor arrivals. Several aspects require modelling to represent the arrivals adequately, these are:

- (1) The time of arrival (or the number of arrivals in a certain time period); and

- (2) The characteristics of the arrivals and any inter-dependencies between these characteristics.

The characteristics that influence patient outcomes were determined when creating the models which capture the transitions between different states (Sections 4.4.2 and 4.5.2). It was these patient and donor characteristics which needed to be taken into account within part (2) of the analysis described above.

The following methodology is implemented when capturing patient and donor arrivals into the liver transplantation system.

Arrival Times

Donor arrivals are expected to occur at random and independently of one another, therefore a Poisson process should provide a suitable means of modelling their rate of arrival (Winston 1994). Similarly a Poisson process should also be applicable to the rate of patients arriving on the waiting list for their first transplant (those arriving for successive transplants are generated through the “re-listing transition” as described in Section 4.5.1). Stat::fit was used to identify the most appropriate distribution to capture the arrival times.

Assignment of Characteristics

When patients or donors arrive into the system a set of characteristics must be assigned to them. These characteristics (or attributes) will help to determine which patient will receive the donated liver and the eventual outcomes

experienced by the patients. The attributes that require assigning are therefore the covariates from the survival and competing risks models and the factors which the allocation policy uses to determine which patient is allocated a donated liver (e.g., transplant centre, transplant urgency, blood group). There will also be inter-dependencies between attributes (e.g., patients requiring a super urgent transplant status will not have liver cancer), and these dependencies need to be taken account of when assigning the attributes on arrival.

Three statistical techniques were used in determining the dependencies between attributes. The technique used was dependent on the nature of the two attributes under consideration;

- (1) The Chi-Squared Statistic was calculated for the relevant contingency table where both attributes took on discrete values;
- (2) The t-Statistic was calculated in comparing means where one attribute took on continuous values and the other discrete values; and
- (3) The Pearson Correlation Statistic was calculated for cases where both attributes took on continuous values.

3.6.2 Assessment Outcome Model

Assessment Rules: Referral to join/not join the waiting list

Logistic regression is used to predict whether an event will take place or not, and to identify the variables that contribute significantly to this prediction. It allows for the modelling of dichotomous outcomes and is applied here to patients who

were referred to the Birmingham Liver Unit, with the outcome of interest being whether they are selected for the waiting list (1) or not (0), (Centre for Applied Statistics, Lancaster University).

Model Development

The logistic regression models were created using SPSS using the forward stepwise regression procedure, with entry value set to 0.05 and removal value set to 0.10. Under these criteria the model is built up by adding one covariate at a time, to decide if a particular covariate should enter into the model in addition to the previous x variables, a comparison is made between Model A (which contains x covariates) and Model B (which contains $x+1$ covariates). If the score statistic implies that Model B is better than Model A at the 95% significance level, then the covariate is included within the model. After a new covariate has been introduced into a model, a check is made to make sure that all the covariates in the model still improve the model – this is tested by omitting each covariate and checking that the inclusion of the covariate significantly increases the accuracy of the model (test at the 90% level using the Likelihood-Ratio statistic). Tough entry and removal values (0.05 and 0.10) were implemented to make sure only variables that were significant in the overall outcome were included in the resultant models.

Goodness of Fit

The developed models were analysed for their goodness-of-fit by using the following statistics to assess the models' capability for adequately capturing the outcomes:

- **The Percentage of Correct Classifications** - which assesses the performance of the model created by calculating the percentage of patient outcomes correctly classified by the model;
- **Cox and Snell R^2 Statistic** - which quantifies the percentage of variation in the response that is explained by the model. The R^2 statistic cannot be computed exactly for logistic regression models, but SPSS computes approximations to these, which can be used; and
- **Hosmer and Lemeshow Test (significance)** - at each step, this is a goodness-of-fit test of the null hypothesis that the model adequately fits the data. If the null is true, the statistic should have an approximately chi-square distribution with the displayed degrees of freedom. If the significance of the test is small (i.e., less than 0.05) then the model does not adequately fit the data (Garson 1998).

3.6.3 Waiting List Outcome Model and Post Transplant

Outcome Models

Survival Time Generation

Survival analysis and competing risks techniques are appropriate for modelling outcomes from the waiting list and outcomes from transplantation because:

- (1) Both situations have a well-defined time origin, these are:
 - a. The time the patient joined the waiting list; and
 - b. The time at which a patient received their transplant.
- (2) The outcomes of interest are the times to certain events occurring (defined as end points in survival analysis and competing risks):
 - a. From joining the waiting list, the times to transplantation, death, or removal ; and
 - b. From receiving a transplant, the times to either re-listing or death and graft failure.
- (3) Not all the events will have been observed by the end of our data collection period (this is called *censoring* and was explained in more detail in Chapter 2 Section 2.4).

Survival or competing risks models were created to capture all the outcomes modelled in Hepatica, as reported in Sections 4.4 and 4.5. SPSS , S-Plus and MS Excel, software packages were used along with the development process outlined next.

Model Development - Choice between Survival Modelling and Competing Risks Modelling

There are several decisions which must be made when developing the models that estimate the times that patients spend in particular states. As already discussed in Section 2.4 the first is to decide whether a survival model or a

competing risks model is more appropriate. This decision can be made by determining whether the following assumption holds:

The survival times are independent of any mechanism that causes the individual's survival time to be censored.

If this assumption holds then survival analysis is appropriate, if it does not hold then competing risks analysis is more appropriate. This assumption can be tested using Equation (2.8) as described in Section 2.4.3.

Survival times need to be estimated once a new patient joins the waiting list, and once a patient receives a transplant. From both these stages, patients can experience one of several events which are of interest:

- (1) The next event that a patient may experience after joining the waiting list, is one of either Death, Removal, Transplantation, or Suspension; and
- (2) The next event that a patient may experience after receiving a liver transplant, is one of either Death, Graft Failure, or Re-Listing back on to the waiting list.

When analysing the available data it is likely that many of the times to these events are censored due to common causes. This might mean that the assumption required for the survival models (that times which are censored need to be independent of cause) does not hold, and competing risks modelling is more appropriate.

Model Development - Survival Model Development Process

Section [A] describes the preliminary analyses performed to identify which type of survival model (PH or AFT as introduced in Sections 2.4.1 and 2.4.2) was appropriate for capturing the survival times. Section [B] goes on to outline the process by which parametric survival models were developed, and how this can be extended to create a competing risks model. Section [C] describes how the goodness of fit of the models developed, was assessed.

[A] Preliminary Analysis

The main aims of this analysis were to identify which type of survival model(s) (PH or AFT) appropriately captured the features of the data and to identify which covariates resulted in significantly different survival curves, across their respective levels. The tests [A.i]-[A.iii], were performed for all the covariates identified as relevant outcomes drivers from the different stages. The analysis also helped to decide whether a stratified model was necessary (i.e., different models for different covariate values e.g., two separate models by transplant urgency status (super urgent and routine)).

[A.i] To identify if the Proportional Hazards (PH) assumption was met, the log cumulative hazard function is plotted against log time (Log-Cumulative Hazard Plots), stratified by each covariate level. The log cumulative hazard function is calculated based on the Kaplan-Meier (K-M) estimate for survival.

If the PH assumption holds, the vertical distance between the curves is constant (as shown in Figure 3.5). For the Weibull model to be appropriate, a series of straight parallel lines, would emerge. Where the lines have slope 1, an Exponential model would be appropriate.

If lines are parallel but not straight, then a non-parametric (Cox) regression model would be appropriate. However, for use in the simulation we need a parametric distribution.

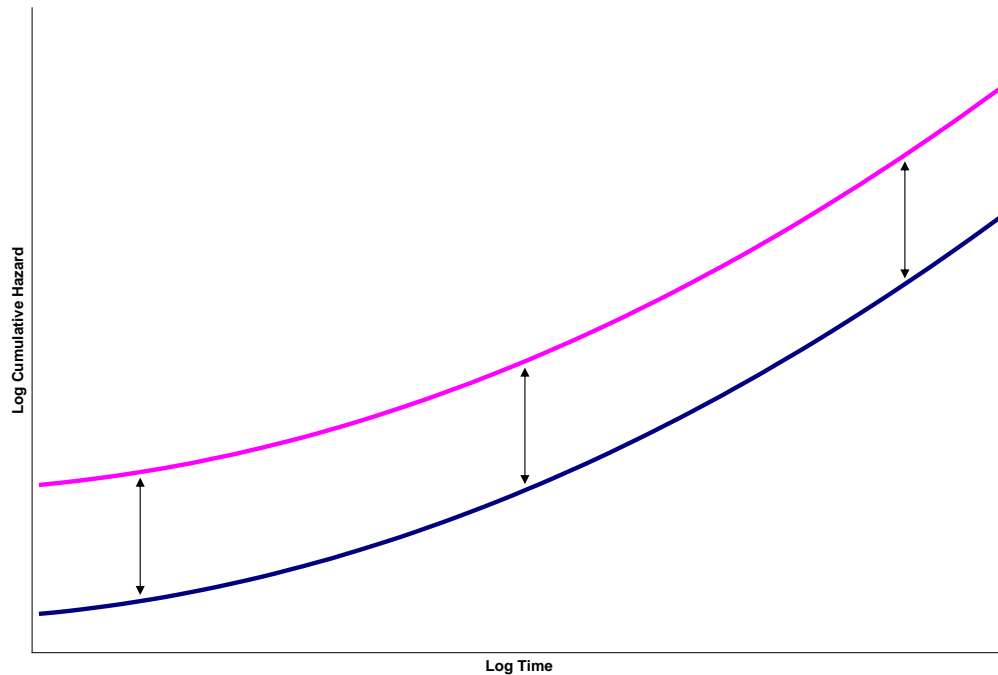


Figure 3.5 Example of curves that satisfy the PH assumption.

[A.ii] To identify if the Accelerated Failure Time (AFT) assumption was met, the cumulative hazard (again estimated using K-M estimates for survival) is plotted against log time (Cumulative Hazard Plots), stratified by each covariate level.

If the horizontal distance between the curves (as shown in Figure 3.6) is constant (i.e., through log time) then an AFT model is suitable for modelling purposes. Steps [A.ii.a] and [A.ii.b] were then employed to identify which of a log-logistic AFT model or a lognormal AFT model would be more appropriate.

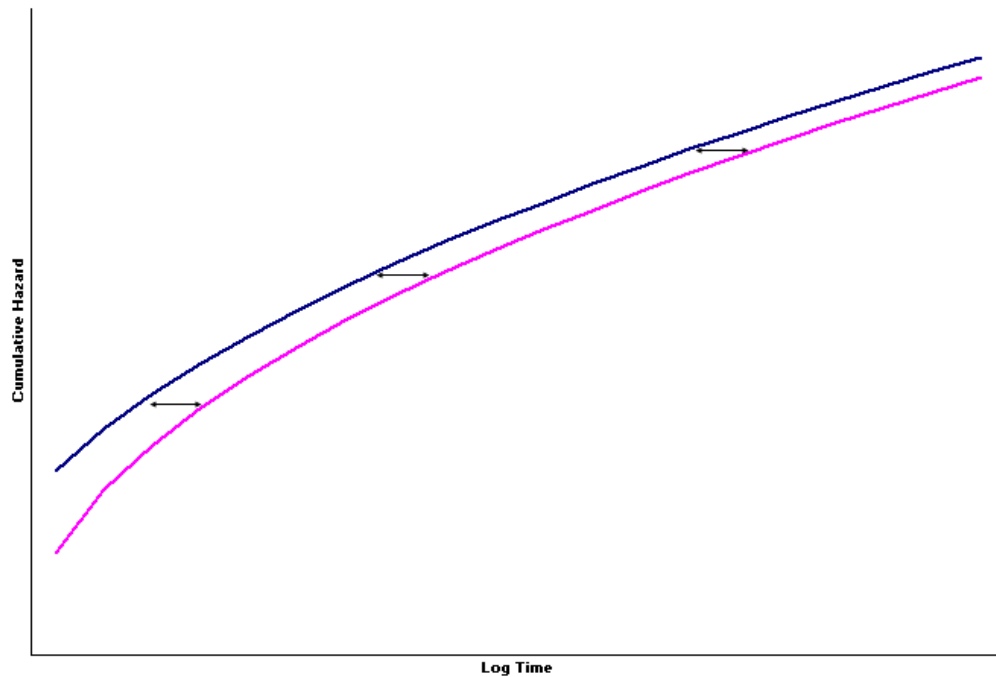


Figure 3.6 Example of curves that satisfy the AFT assumption.

[A.ii.a] To test the appropriateness of a log-logistic AFT model, the log odds against log time graph was plotted (Log Odds Plots), stratified by each covariate level.

If the lines obtained were parallel and straight then the log-logistic AFT model was suitable. If the lines were straight but not parallel then a stratified log-logistic AFT model was applicable. If the lines were parallel but not straight then another proportional odds model was applicable.

[A.ii.b] To test the appropriateness of a lognormal AFT model, the $\Phi^I(1-S(\text{Time}))$ by $\text{Log}(\text{Time})$ graph was plotted, stratified by each covariate level. If the lines obtained were parallel and straight then a lognormal AFT model was suitable.

[A.iii] Log Rank and Wilcoxon test statistics: To test for differences between the survival distributions of the different patient groups the test statistics *Log Rank* and *Wilcoxon test* (also known as the *Breslow Test*) statistics were also analysed, to determine which covariate values lead to significantly different survival curves. The Log Rank statistic was calculated where the PH assumption applied and the Wilcoxon statistic where the AFT assumption applied.

[B] Parametric Model Development Process

The following process was used in creating parametric distributions which were identified at stage [A] as potentially suitable in capturing the outcome being considered.

Null⁸ models were first created for each of a set of the potentially suitable parametric distributions. Then the $-2\log\hat{L}$ statistic was used to assess the agreement between the model and the data (Collett 2003). The statistic is based on the maximised likelihood \hat{L} value of each model. For a given set of data, the

⁸ A *null model* is one that contains no explanatory covariates in the linear component of the model, hence the model does not attempt to distinguish between two groups of patients.

larger the value of the maximised likelihood, the better the agreement between the model and the observed data.

The following covariate selection procedure was used:

- a) Fit survival models that contain each of the covariates one at a time. Compare these models with the null survival model using the $-2\log\hat{L}$ values obtained. (Here the null models are used as a basis for comparison and in this step to help identify whether a particular parameter improves the fit of the model significantly).
- b) Fit the covariates that appear significant at step a), together. Keep in the model those that significantly increase the $-2\log\hat{L}$, omit those that do not. Drop each covariate in turn and check the effect of omitting each.
- c) Add the covariates not significant in step a) to the model from step b) and check if they are now significant, in the presence of other covariates.
- d) Check that no term can be omitted without significantly increasing the value of $-2\log\hat{L}$, and that no term included significantly reduces $-2\log\hat{L}$.

A rigid application of a particular significance level was not used and also decisions on whether to include or to omit a covariate were based on significance levels which allowed covariates to easily enter the model (Collett 2003). The covariates counted as significant at step a) are those significant at least at the 85% level, and for the rest of the stages, the significance level was taken to be 90%. Using a manual selection procedure as opposed to an

automatic one, provided more control over which covariates to include in the model, when there was a choice of bringing in more than one covariate.

Model Development - Competing Risks Model Development Process

Competing risks modelling is not as standard as survival analysis and standard software packages do not include routines which perform this analysis. In their paper (Lunn and McNeil 1995) outline a methodology in which a dataset can be adapted to allow for a form of competing risks analysis to be implemented through using standard statistical packages. However, their approach makes the assumption that the risks being considered are independent of one another. This may not be true for the outcomes from the waiting list, as if a patient is likely to die soon then they might receive a higher priority for transplantation, and hence transplantation time will be dependent on death time.

This approach does allow for the modelling of competing risks and was implemented when developing the competing risks models, in conjunction with the process outline in [A] and [B]. For stage [A] instead of plotting by covariates, for the CR models the plots were by outcome (Hemming and Anzures-Cabrera 2006). This identified if a PH model or an AFT CR model was appropriate. Lunn and McNeil (1995) have applied their methodology to the Cox regression model. Here it has been extended to include parametric models for the underlying hazard function.

[C] Goodness of Fit

To evaluate how well a particular survival model or competing risks model captured the outcomes observed in the data, Cox-Snell residuals⁹ were analysed (more details are presented in Appendix H), and plots of the K-M estimate were compared to the fitted models.

[C.i] Cox-Snell residuals: Cox-Snell residuals, r_{C_i} , were used to analyse the model fits. The way in which to calculate the residual depends on the distribution being considered, and the different forms are presented in Appendix H. The Kaplan-Meier estimate of the survivor function of the Cox-Snell residuals, denoted $\hat{S}(r_{C_i})$, was obtained and $-\log \hat{S}(r_{C_i})$ was plotted against r_{C_i} . A straight line with unit slope and zero intercept resembles that the fitted model is appropriate (Collett 2003). A test was also performed to determine which model approximated a straight line closest to one with unit slope through the origin, by using linear regression.

[C.ii] Plots of Kaplan-Meier Survival and the Estimated Model: Kaplan-Meier curves were plotted along with the fitted model to help in visualising the fit of the model developed, against the observed data.

⁹ Note: residuals can only be calculated for the patients that have experienced the outcome being modelled. The patients whose values are censored are therefore not plotted, when analysing residuals (Collett 2003).

3.7 Data used for the Sub-Models

3.7.1 Description of the Data

Assessment Stage Data

Information about patients who are referred to a liver unit is only available from that individual liver transplant unit. The data analysed for this thesis were collected from Birmingham Liver Unit (BLU), and consist of all adult patients (aged 16 and above) who were referred to BLU between 1st January 1999 and 31st December 2002. Of interest was whether or not they had been given a place on the waiting list. These data were used to develop an understanding about which patients are likely to be placed on the waiting list following referral to a liver unit, and whether certain patient characteristics play a significant part in the decisions made.

Transplant Data

Information about all patients who join the waiting list is available from UK Transplant. For this thesis, data was obtained for all adult patients (aged 17 or older) who joined the UK liver transplant waiting list between 1st January 1999 and 31st December 2002. Details of their patient history were recorded up to 6th October 2003.

Information about liver donors is also available from UK Transplant. Data were provided on all donors whose livers were transplanted into adult patients between 1st January 1999 and 31st December 2002.

These data were used to develop an understanding about the life expectancy of patients on the liver transplant waiting list, and which patient characteristics are the strongest predictors of this. Similarly, the data were also used to estimate life expectancy post-transplant based on patient, donor, and transplant characteristics.

3.7.2 Risk Factors

In order to model patient and donor arrivals, and patient transitions it is necessary to determine the arrival distributions, activity time distributions, and the risk factors that drive these. An initial list of risk factors was determined by looking at previous literature, obtaining the opinions of medical experts, and researching how the system currently operates by consulting UKT documentation (UK Transplant 2001a). The factors considered were then restricted to data attainable from UKT and BLU and covered 4 main categories: Patient Demographics, Donor Related Measures, Transplant Related Measures, and Clinical Measures. The risk factors identified were different for the pre-waiting list and post-waiting list models, and are explained in more detail below.

Assessment Stage Risk Factors

The factors considered in pre-transplant models are summarised in Table 3.8. The first factor considered is primary liver disease, since different diseases will affect patients over various timescales. A study analysing the French liver transplant waiting list identified transplant urgency and region (geographical

location of the patient) as being key predictors in determining the life expectancy of a patient on the waiting list (Suc *et al.* 2000).

The MELD score, measures the severity of illness for chronic liver disease sufferers and it is currently used in the US to determine who should receive a donated liver (Wiesner *et al.* 2003). The score replaces the Child-Turcotte-Pugh score which had been used previously (Wiesner *et al.* 2001). The MELD score relies on more objective measures (which are based on clinical tests) and has been found to accurately predict short-term mortality from liver disease (Kamath *et al.* 2003), and more accurately than the Child-Turcotte-Pugh score (Wiesner *et al.* 2003). The MELD score has also been found to be successful at predicting mortality across a range of chronic liver diseases (Said *et al.* 2004). Other factors considered include patient gender (Fink *et al.* 2007), and patient age.

Table 3.8 Pre-Transplant Risk Factors Considered in the Analysis.

Pre-Transplant Risk Factors	
Patient and Disease Related Characteristics	Primary Liver Disease at Registration
	Transplant Urgency
	MELD score
	Gender
	Patient Age at Registration
Geographical Location	Centre

Transplant Risk Factors

Post-transplant risk factors also include donor characteristics and transplant characteristics. The requirement for this thesis is to investigate medium to long-term survival of patients post-transplant, since we want to determine the effect of a policy on the total number of life years gained. Many studies have previously concerned themselves with determining short-term outcomes (Avolio

et al. 2004). Studies have been performed to identify factors affecting post-transplant survival (Adam *et al.* 2000; Angelis *et al.* 2003; Gonzalez *et al.* 1994; Lin *et al.* 1998).

Table 3.9 Post-Transplant Risk Factors Considered in the Analysis.

Post-Transplant Risk Factors	
Patient Characteristics	First Transplant
	Primary Liver Disease at Registration
	Recipient Age
	Transplant Urgency
	Recipient Body Mass Index (BMI)
	Recipient Gender
Clinical Characteristics	MELD score
Donor Characteristics	Donor Age
	Donor Cause of Death
Transplant Characteristics	Donor-Recipient ABO match
	Cold Ischaemic Time (minutes)
	Completeness of Liver Used
	Donor-Recipient Rhesus match
	Donor-Gender to Recipient-Gender
	Donor Weight minus Recipient Weight

These studies have identified various factors as key to post-transplant survival. Those which have been identified as appropriate to this work are summarised in Table 3.9. Previous studies have also found that transplant centre-related factors, such as the number of liver transplants performed are significant in determining outcomes (Adam *et al.* 2000). It was decided, however, that there are too few transplant centres in the UK – seven – to be able to make a reliable assessment of this. Other variables that may influence post transplant survival, but were not considered in our analysis due to a lack of data, included: Donor Type (Cadaveric Heartbeating, Cadaveric Non-Heartbeating, Living (related/unrelated), Domino).

Some people would expect that the time spent waiting for a liver transplant would be an indicator as to when a patient will die, however it has been shown (Freeman *et al.* 2000) that waiting time provides a poor indication of actual death time, mainly due to patients joining the waiting list at varying stages of their disease, and so this covariate is not considered in the analysis.

Simplification of Variables

Some of the factors listed in Tables 3.8 and 3.9 took on a number of different values and so had to be simplified. Appendix A lists all the diseases that are indications for transplantation (this list was obtained from UK Transplant). It also shows the groupings which indicate how the diseases were aggregated and simplified so that they could be used in this analysis. The disease groupings implemented were based on a Liver Advisory Group paper (Hudson *et al.* 2005), amended by splitting the Cirrhotic diseases group into smaller groups so that the groups were more comparable in size. The groupings also reflected the disease categories which have been identified as important because their occurrence is likely to increase in the future (Section 1.2.6). Other risk factors which were simplified, are: donor cause of death, MELD score, and patient body mass index (as outlined in Appendix A).

3.8 Experimental Design

Two types of experimental design are commonly employed within simulation experiments; (1) full-factorial, and (2) fractional-factorial (Kelton and Barton

2003; Law and Kelton 2000). However, neither of these approaches is appropriate within the context of this work. Assuming that each factor can take on one of two levels and there are k input factors, the full factorial approach identifies 2^k different combinations of input factors. Within the context of this thesis we have initially defined 4 types of input factors (demand, supply, assessment rule, and allocation rule), which take on a varying number of levels (4, 4, 3, and 17, respectively). This implies a minimum¹⁰ of $4 \times 4 \times 3 \times 17 = 816$ experiments to perform under the full-factorial methodology. This is an extremely large number of experiments to perform and analyse. One approach to limit the number of experiments required is the fractional-factorial design. This approach performs a fraction of all the possible factor-combinations (Law and Kelton 2000), and the levels which are chosen to run are identified at random. This approach is appropriate where the levels are based on ordinal inputs (e.g., identifying the effect of employing 2, 3, 4, or 5 cashiers), but provides a non-intuitive means for this study, as many of the factors are not based on numerical aspects, for example, blood group or centre match. Therefore, a new experimental design, as described below, was developed to analyse which of the experimental factors (as outlined in Section 3.3) most improved the equity and utility measures.

Experimental Design Implemented

The experimental design implemented is as follows:

¹⁰ The number given is a minimum since several of the levels within the allocation factor could be combined to construct new levels, for example, L3 gives priority to patients with a compatible blood group and L6 to patients nationally, combining L3 and L6 would give a policy which gave priority to compatible patients nationally.

- (1) Run the base scenario which assumes the current assessment (A1) and allocation (L2) rules and constant future demand (D1) and supply (S1);
- (2) Run 23 other scenarios in which only one factor level change is made (i.e., run the remaining scenarios outlined in Table 3.10);
- (3) Analyse the results from steps (1) and (2) to identify (using methods outlined in Section 3.4.3) which of the scenarios in step (2) made improvements in the equity and/or utility measures, from the base scenario considered in step (1);
- (4) Join up the allocation policies (where possible) found in (3) to create “alternative” allocation policies for investigation; and
- (5) Run a full factorial experiment using the allocation factors identified in (3) and the most likely future demand and supply factors.

Table 3.10 The Base Scenario and Scenarios where only One Factor Level is Changed.

Scenario	Demand	Supply	Assessment	Allocation
Base scenario	D1	S1	A1	L2
L3	D1	S1	A1	L3
L4	D1	S1	A1	L4
L5	D1	S1	A1	L5
L6	D1	S1	A1	L6
L7	D1	S1	A1	L7
L8	D1	S1	A1	L8
L9	D1	S1	A1	L9
L10	D1	S1	A1	L10
L11	D1	S1	A1	L11
L12	D1	S1	A1	L12
L13	D1	S1	A1	L13
L14	D1	S1	A1	L14
L15	D1	S1	A1	L15
L16	D1	S1	A1	L16
L17	D1	S1	A1	L17
A2	D1	S1	A2	L2
A3	D1	S1	A3	L2
S2	D1	S2	A1	L2
S3	D1	S3	A1	L2
S4	D1	S4	A1	L2
D2	D2	S1	A1	L2
D3	D3	S1	A1	L2
D4	D4	S1	A1	L2

3.9 Summary

This chapter started by summarising the key reasons and objectives for modelling the UK Liver Transplant System. It outlined all the methods which are implemented in developing a model for capturing the assessment and allocation phases, in order to understand how changes within these phases affect the overall outcomes experienced by patients.

Hepatica is also designed to incorporate the experimental factors (inputs) which capture future demand, future supply, alternative assessment rules and alternative allocation rules. These input factors are based on the likely or viable changes which may affect the UK system.

Hepatica allows the measurement of key equity and utility outputs. A methodology for the comparison of equity and utility outputs from the various scenarios (as defined by the input factors, Section 3.3) is constructed, to enable evaluation of any improvements made by the new scenarios (in particular, new assessment and allocation rules). The utility measures considered are:

- Life years in the system per patient;
- Life years gained per transplant;
- The percentage of patients re-listed within 1 year of receiving a transplant;
- The percentage of patients to experience death or graft failure within 1 year of receiving a transplant; and
- The percentage of patients to experience death or removal from the waiting list, and the number of livers wasted.

The level of equity within the system was also considered by looking at the outcomes that different patients experienced following their arrival onto the waiting list, and post-transplant.

This chapter also outlined the specific processes, tests and risk factors employed in developing the relevant sub-models. It also explained the techniques used to test the adequacy (i.e., goodness-of-fit) of the models developed.

The experimental design used to run the various scenarios in Hepatica was also presented. Normal strategies, such as, full-factorial and fractional-factorial designs were explained not to be applicable in this study and therefore a new approach has been constructed.

Chapter 4

Statistical Sub-Model Development

4.1 Introduction

This chapter outlines the development of the sub-models which are used within Hepatica to determine the flow of patients through the liver transplantation system and the arrival of donated livers. The flows and arrivals help to maintain a liver transplant waiting list and determine the outcomes experienced by the patients. As a result of the analyses described in this chapter, the structure of Hepatica shown in Section 3.5.1 is reassessed.

4.2 Statistical Sub-Model Development Process

The general process of model development incorporated the steps outlined in Table 4.1, below.

Each model type (e.g., logistic regression model, survival model) requires slightly different procedures within some of the steps, in particular within steps 6 and 7, and these were elaborated on in Sections 3.6.2-3.6.3.

Table 4.1 Overall Sub-Model Development Process.

Step	Overall aim of the step	Questions to be answered
(1)	Identification of required models.	What transition or arrival requires modelling? Why does it require modelling?
(2)	Identification of data required and where to obtain the data from.	What data is required? What stage of the liver transplantation process will this data come from? Where will this data be obtained from?
(3)	Initial cleaning of the data, to eliminate any erroneous entries.	Are there any inconsistencies and inaccuracies within the data? Are missing values obtainable from other data sources?
(4)	Initial data analysis and data restructuring, to aid with understanding features of the data.	Are there any additional covariates or recalculated covariates required? Do any of the variables need to be grouped? Basic descriptive analyses utilised to identify what distributions the various covariates had (e.g., shape of age/weight distributions). Are there any dependencies that we need to be aware of?
(5)	Identification of relevant mathematical modelling approaches.	What mathematical modelling technique is appropriate and why?
(6)	Model development.	Which models need developing?
(7)	Evaluation of the “goodness-of-fit” of the models developed.	How accurately do the developed models capture the data? Which model is the <i>best</i> in capturing this particular transition or arrival?

Some of the steps in Table 4.1 (steps 1, 2, 5, 6 and 7) have been discussed in previous chapters and will only be summarised in this chapter. The actions taken in step 3 were similar across all the models which were developed and within this step the data were assessed for any items that may have been inaccurate (outliers, typing mistakes). This was done by checking the values present in the datasets and making sure that they fell into ranges that seemed reasonable. If they did not, the data points were checked at source.

4.3 Assessment Outcome Model

4.3.1 Development

The assessment outcome model attempts to capture the patient characteristics that influence which patients “join the waiting list”. Logistic regression was identified as being the appropriate modelling technique to capture these outcomes (Section 3.2.3). The data required to create this sub-model are only held at individual liver units (Section 3.7.1); in this case the data used were obtained from Birmingham Liver Unit. Patients referred to a liver transplant unit with liver failure are placed on a national waiting list if deemed by their consultant to meet the assessment criteria (Section 1.3.4). The likelihood of a referred patient being placed on the waiting list is dependent on individual patient characteristics (e.g., age, liver disease, urgency, as summarised in Section 3.7.2). Table 4.2 summarises the data regarding these characteristics that were available for analysis.

The data was structured with an indicator that represented whether or not a particular patient had been placed onto the waiting list; this indicator represented the response variable of the logistic regression model. Of the 736 patients to be referred to Birmingham Liver Unit within the observation period, 62.4% were eventually placed on the waiting list.

Table 4.2 Covariates considered in the Assessment Outcome Model.

Covariate	Appropriate Values	Discussion
Gender	Male, Female.	The prognosis for many diseases varies by gender.
Age	Age in years.	The UK Transplant guidelines determine the age of an adult as 17 for listing onto the waiting list. However, before the patients can be listed, they need to go through an assessment phase, hence 16 year olds are also considered in this part of the analysis.
Primary liver disease	Disease groups as outlined in Section A.1.2 (Appendix A).	The primary liver disease will influence prognosis and is also one of the variables by which assessment and allocation decisions can be changed.
MELD score	Both as a continuous value based on the original score, and as a factor variable as explained in A.3 (Appendix A).	MELD score measures the severity of a chronic liver disease (Section 2.2.2).
Transplant urgency	Routine, Super Urgent.	Will influence how quickly a patient is assessed.

Model Development

Initially, a decision had to be made as to how to utilise the available MELD scores. Firstly, they are only applicable to chronic liver disease patients. Secondly, there is the option to either treat them as a single continuous variable, or to group the scores together to leave four factor variables (as explained in Section A.3, Appendix A). Three approaches were therefore trialled in modelling the outcome from referral, and these are summarised in Table 4.3. Appendix I reports on the details of the development of these models.

Table 4.3 Approaches Analysed for the Assessment Outcome Model.

Approach	Super Urgent/Acute Patients	MELD Score as a independent variable
A	Included when developing the logistic regression model	Excluded the MELD score in the analysis
B	Excluded when developing the logistic regression model	Included the MELD score as a continuous variable
C	Excluded when developing the logistic regression model	Included the MELD score as factor variables

Analysis of the data showed that 95.3% of all super urgent/acute patients were placed on the waiting list. For models B and C it was assumed that *all* super urgent/acute patients were listed onto the waiting list, and the MELD score is only used as a factor for the remaining patients who are suffering from chronic liver disease (since the score is not applicable to patients with super urgent or acute liver diseases).

Goodness-of-Fit

The goodness-of-fit tests used are summarised in Table 4.4. The percentage of correct classifications is defined as:

$$\frac{a + b}{N} \quad (4.2)$$

where a = number of observed patients not listed & to have a calculated response value of “0” from the model,

b = number of observed patients listed & to have a calculated response value of “1” from the model,

N = the total number of patients.

Table 4.4 Goodness-of-Fit Tests the Assessment Outcome Model.

Approach	Variables present in the final logistic model	All Super Urgent patients assumed to be listed?*	Correct classifications (%)	Cox and Snell R ² statistic	Hosmer and Lemeshow test (significance)
A	Super Urgent/Acute Liver Disease Unknown Liver Disease Cryptogenic Liver Disease Alcoholic Liver Disease Hepatitis C Age	No	69.0 (logistic model for all patients)	0.14	0.82
B	Unknown Liver Disease Cryptogenic Liver Disease Alcoholic Liver Disease Hepatitis C Age MELD score	Yes	66.2 (logistic model for routine patients) + $95.3 \times \frac{61}{736}$ (super urgent cases) = 74.1	0.10	0.98
C	Unknown Liver Disease Cryptogenic Liver Disease Alcoholic Liver Disease Hepatitis C Age MELD group 2	Yes	66.2 (logistic model for routine patients) + $95.3 \times \frac{61}{736}$ (super urgent cases) = 74.1	0.12	0.76

* when all super urgent patients are assumed to be listed, they were excluded from the development of the logistic regression model and the last two columns report statistics for just the logistic regression model which considered just the routine patients.

4.3.2 Final Model

From Table 4.4 we can see that Approach B provides the best fit, since it classifies the greatest percentage of patients into the correct outcome groups (compared to the observed outcomes), explains roughly the same amount of

variation as the other models, and the model fits the data most closely when considering the Hosmer and Lemeshow test. Table 4.5 outlines the details of this logistic regression model and Figure 4.1 presents a box plot of the predicted probabilities by the observed outcomes, of those suffering from Chronic Liver Diseases.

Table 4.5 Logistic Regression Model B - for capturing the Assessment Outcomes for Chronic Liver Disease Patients.

Covariate	B/coefficient	Significance of Wald statistic	Exp(B)
Age	- .022	.007	.978
Unknown Liver Disease	- 1.503	<0.001	.222
Cryptogenic Liver Disease	- 1.068	<0.001	.344
Alcoholic Liver Disease	- 1.457	<0.001	.233
Hepatitis C	- .594	.014	.552
MELD score	- .026	.021	.974
Constant	2.641	<0.001	14.021

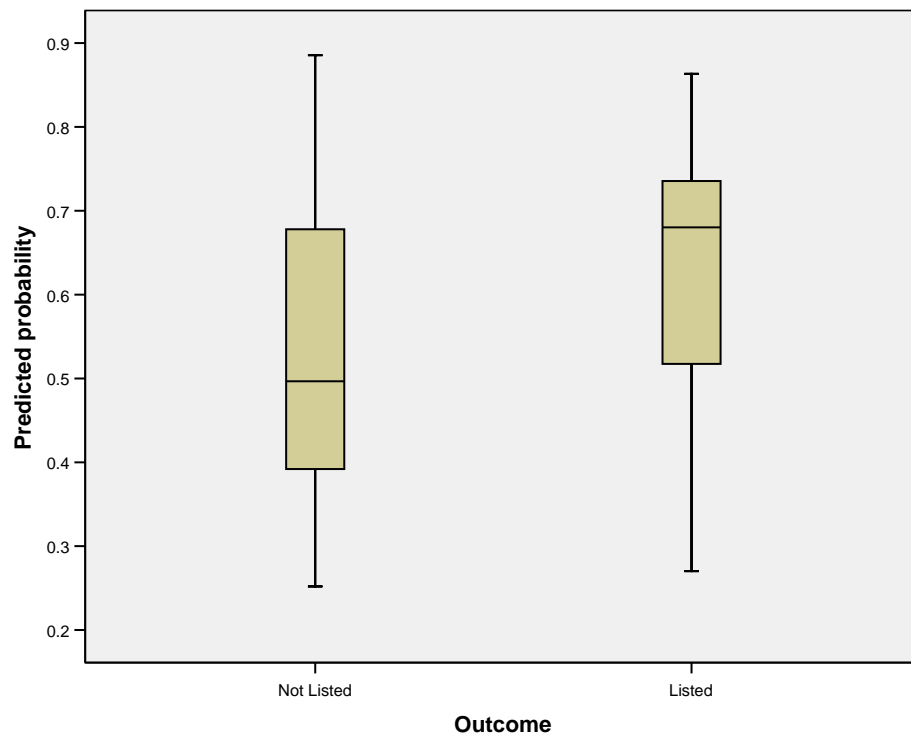


Figure 4.1 Box Plot of the Predicted Probabilities as Estimated using the Final Model from Approach B, by the Observed Outcomes of Not Listed or Listed.

Interpretation and Evaluation of the Resultant Model

From the model details in Table 4.5 (column 3), we can see that each of the variables present in the final model are significant at the 95% level. The model helps us to identify some key factors which influence whether or not a patient suffering from chronic liver disease joins the waiting list. All the coefficients of the factors are negative which means that:

- (1) As the age of the patient increases the patient is less likely to be placed on the waiting list (the likelihood of being listed decreases by 2.2% for every 1 year increase in patient age). This seems a reasonable representation since older patients may be less likely to be listed onto the waiting list, as they are more likely to have complications (other illnesses) which may make a liver transplant less viable;
- (2) If the patient had an illness that falls into one of: unknown liver disease, cryptogenic liver disease, alcoholic liver disease and hepatitis C, they are less likely to be placed on the waiting list (by 77.8%, 75.6%, 76.7%, and 44.8% respectively) than those not diagnosed with any of these diseases. This is a reasonable approximation, since patients with alcoholic liver disease are assessed to more stringent criteria which will restrict the number who join the waiting list. Hepatitis C patients may also miss out due to the likelihood of their disease recurring. There may be uncertainty as to the benefit to be gained from a liver transplant where the cause of liver disease is unknown; and
- (3) As the MELD score (continuous values) increases by 1 unit the patient is 2.6% less likely to be placed onto the waiting list. Table 4.6 shows how the

likelihood of being listed onto the waiting list by MELD group, from the observed data. From groups 2, 3, and 4, the model applies as the probability of listing is decreasing. However, group 1 patients are less likely to be listed than group 2 patients, and this is contrary to what the logistic regression model predicts. This contradiction could be due to dependencies between other factors which are consider in the model and also due to only 95 patients having a MELD score captured by MELD group 1, while 576 patients had MELD scores represented by the other groups.

Table 4.6 Percentages of Patients observed as listed within the Birmingham data, by MELD Group.

Group	% Listed within Group	Total Number in Group
MELD 1	55.2	95
MELD 2	68.0	379
MELD 3	50.4	156
MELD 4	47.4	41
Super Urgent Patients	95.3	65

4.3.3 Overall Evaluation

Overall, it was not possible to provide a convincing statistical analysis of the selection procedure for the waiting list for patients with ESLD. From Figure 4.1 it can be seen that the resultant model does not adequately differentiate between patients who joined the waiting list and those that did not. There were several limitations to the analysis performed and hence the use of the logistic model was not accurate in capturing the overall outcome. The key issues were:

- No adequate differentiation between those placed on the waiting list and those that are not. Only 74% were correctly placed through using a logistic

- regression model to predict the outcome for the chronic liver disease sufferers and by assuming that all super urgent patients were listed;
- Limited data were available: MELD score, age, disease groups, gender. Pre- and post-transplant life expectancies, on which the decision to list a patient on the waiting list is based, were not truly captured. These measures were hard to obtain as consultants are not given specific guidelines on how to assess the survival pre- and post- transplant. Patients are placed on the waiting list when their consultant broadly feels that they fit the survival criteria outlined in the assessment criteria (as detailed in Section 1.3.4); and
 - The patient mix, in terms of disease groupings and age distributions that joined the waiting list from Birmingham Liver Unit is not statistically similar to the patient mix that joined the waiting list from all over UK (as analysed in Appendix I, Section I.4).

As a result it was decided to abandon the plan to create a model to represent the assessment phase. Instead, analysis was performed on patients who arrived straight onto the waiting list (as described in Section 4.6) and the information from this allowed for the generation of patient characteristics and arrival rates, within Hepatica. Changes to the assessment criteria can still be simulated by changing the rate of arrivals, and the prognoses of patients who are placed on the waiting list. This would provide a rudimentary way in which to evaluate the likely impact of any changes to the assessment process.

The revised model structure of Hepatica is depicted in Figure 4.2 below.

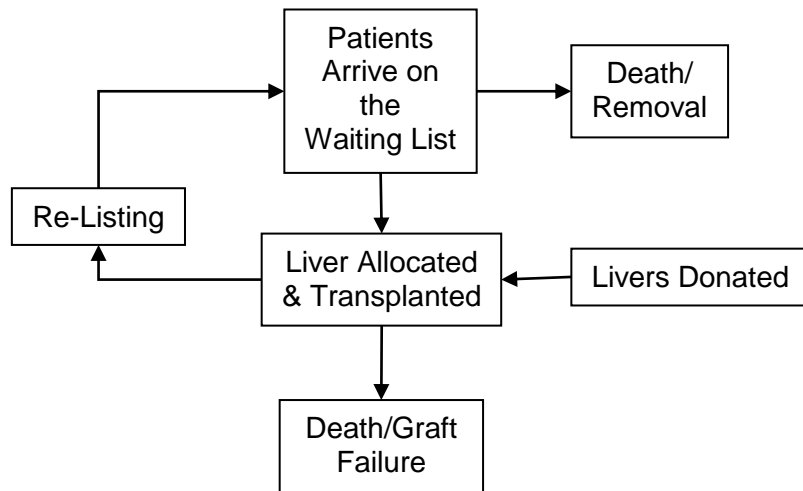


Figure 4.2 Revised Flow Diagram of Events Captured in Hepatica.

4.4 Waiting List Outcome Model

4.4.1 Development

Once a patient joins the waiting list there are a number of different outcomes that they can experience. Most patients will either receive a transplant, or will die. Some will be removed from the waiting list completely, while others will be suspended for a short period.

Suspension refers to the situation where a patient is taken off the waiting list temporarily, perhaps because they are suffering from another illness and must recover before they will have a realistic chance of surviving the transplantation process. The intention is that all patients who are suspended from the waiting list will re-join it at some point. As such, it is not the final outcome for the vast majority of patients. Table 4.7 below indicates that of all the patients who joined the waiting list between the start of 1999 and the end of 2002, only four patients were recorded as suspended on 6th October 2003. No information is available about the number of patients who were suspended and then re-joined

the waiting list, which means that it is not possible to model this event with any accuracy. This outcome was therefore omitted from the model.

Table 4.7 Frequencies of eventual patient outcomes from the waiting list.

Status	Patients who joined the waiting list from 1/1/99 to 31/12/02, as known on 6/10/03	
	Number	Percentage (%)
Transplanted	2049	83.5
Removed	181	7.4
Dead	208	8.5
Suspended	4	0.2
Active*	11	0.4
Grand Total	2453	

** patients still on the waiting list as on 6/10/03*

The time until transplant is dependent on the allocation policy in place and the characteristics of the donors and patients. As such, it is not a transition that needs to be modelled explicitly, although it would be expected that the modelled times to transplant should be comparable to those experienced in reality.

The key requirement for Hepatica is therefore to estimate transition times to removal and/or death from the point that a patient joins the waiting list, and how these are dependent on the characteristics of the patient.

Information about the outcomes experienced by patients once they have joined the liver transplant waiting list is obtained from UK Transplant (Section 3.7.1). The dependent variables analysed were the different outcomes experienced and the time until these occurred. The patient characteristics previously discussed in Section 3.7.2 (and listed in Table 4.8 below) are those covariates believed to influence these outcomes and the transition times between events.

Table 4.8 Covariates considered for the Waiting List Outcome Model.

Covariate	Appropriate Values	Discussion
Primary Liver Disease	Disease groups as outlined in Section A.1.2 (Appendix A).	The primary liver disease will directly influence prognosis.
Transplant Number	First, Successive.	Patients waiting for successive transplants will in general be more ill.
Gender	Male, Female.	The prognosis for many diseases varies by gender.
Transplant Urgency	Routine, Super Urgent.	Will influence patient prognosis.
Centre Registered at	A, B, C, D, E, F, G.	Different centres may interpret registration criteria slightly differently. Other aspects may vary by centre (e.g., resources) which may influence outcomes.
Age	Age in days.	Older patients may suffer from illnesses other than liver disease.

The most likely reason for a patient being removed from the waiting list is that the patient has become too ill to benefit from a transplant (i.e., their life expectancy is very low). This implies that the outcomes of death and removal are closely related – both events occurring if the patient becomes very ill – and so the groups of patients experiencing each of these outcomes are likely to be very similar. Three outcomes were therefore modelled and investigated: (1) death, (2) removal, and (3) death or removal. This third outcome, and the reasons for considering it, are discussed in more detail in the segment below on Model Development. Ultimately the decision to be made is whether these two events can be modelled as one, or if they need to be modelled separately.

Model Development

Basic descriptive analyses were utilised in identifying how the various attributes were distributed. The clearest result from this was that, as expected, the

transition times for super urgent patients were far smaller than for patients waiting for a routine transplant (Table 4.9). This suggests that separate models may be required to estimate the time to death and/or removal for these two groups of patients.

Table 4.9 Average time (days) from joining the waiting list to the outcome experienced by the urgency of transplant.

Urgency	Death or Removal	Transplantation
Routine	90	79
Super Urgent	5	3
Overall	67	66

Figure 4.3 depicts the hazard rate curves (as defined in Equation (2.8)) for the events to transplantation, to death, to removal, and to unknown event (as at the end of the observation period) for all patients who joined the waiting list. The hazard rate curves for the events death and removal are similar and the hazard rate curve for transplant is significantly different. Since the death and removal hazard rates are similar over time, this provides justification that these events may be combined, as they have a similar chance of occurring at any one point in time and are independent of cause. For this reason, the combined event death or removal (censored at transplant) will be modelled instead of the two separate events death and removal.

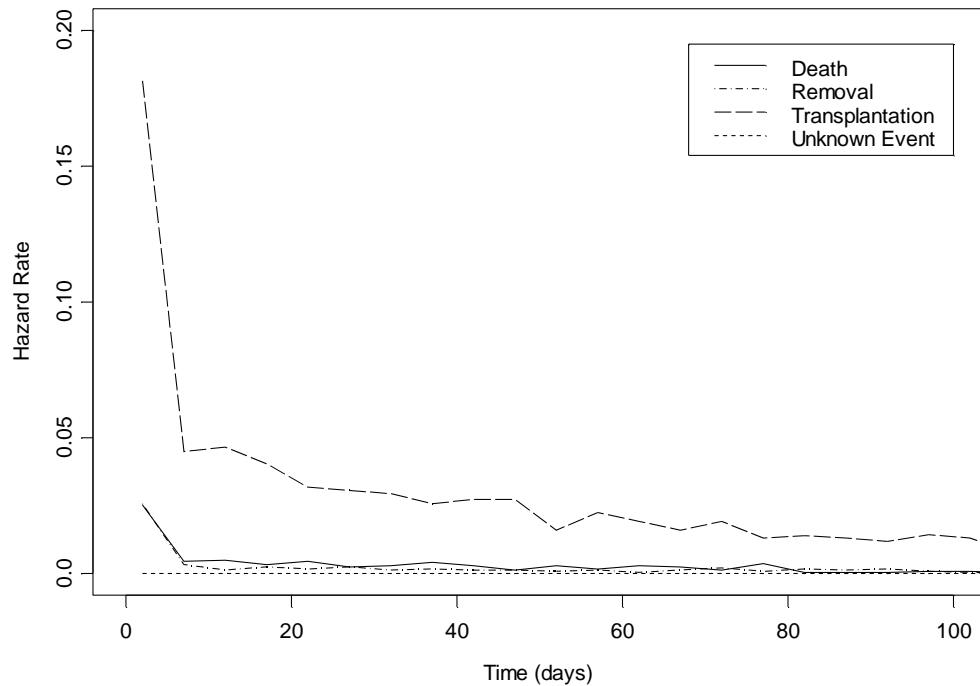


Figure 4.3 Hazard Rates for all outcomes from the waiting list for all patients.

Figures 4.4 and 4.5 show the hazard rates of (1) death or removal, (2) transplantation, and (3) unknown (censored) events, by the urgency of the required transplant. Figure 4.4 shows that most super urgent patients will experience one of these outcomes within the first 5 days. The hazard rates then level off, with very few patients remaining on the waiting list after this time. Figure 4.5 show similar patterns between the two curves, the hazard rates for death or removal, and transplantation declining at a similar rate. This indicates that the two hazards are not independent of one another. This implies that a CR model would be more suitable than a survival model. A CR model was therefore developed as well as the survival model. In addition to capturing death or removal event (as for survival model) it also captures Transplantation and censors the unknown events.

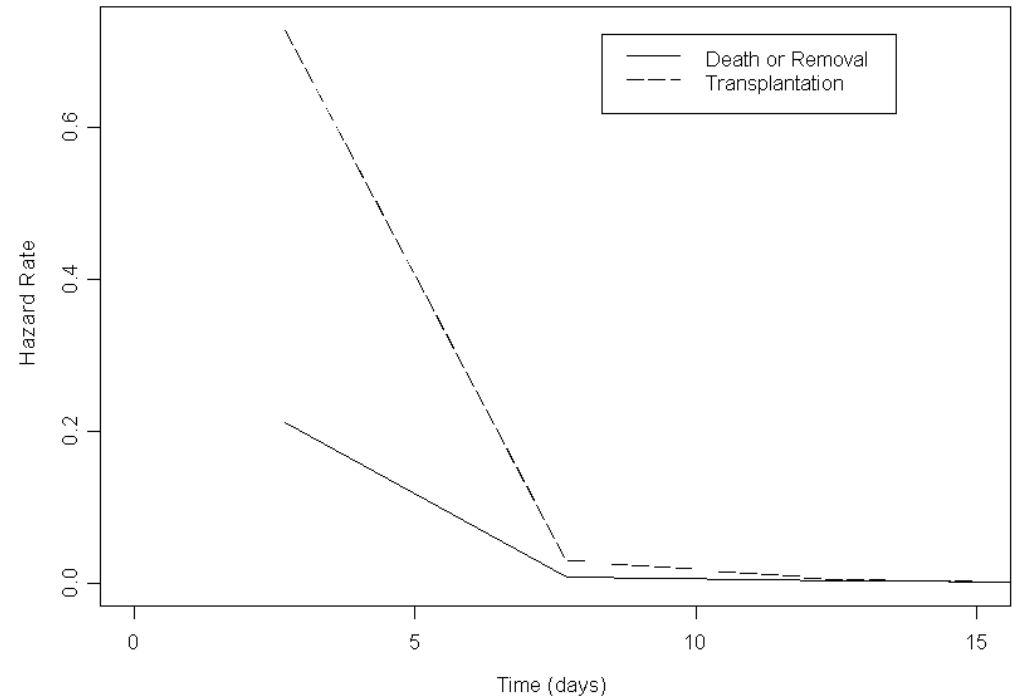


Figure 4.4 Hazard Rates for all outcomes from the waiting list for patients waiting for a super urgent transplant.

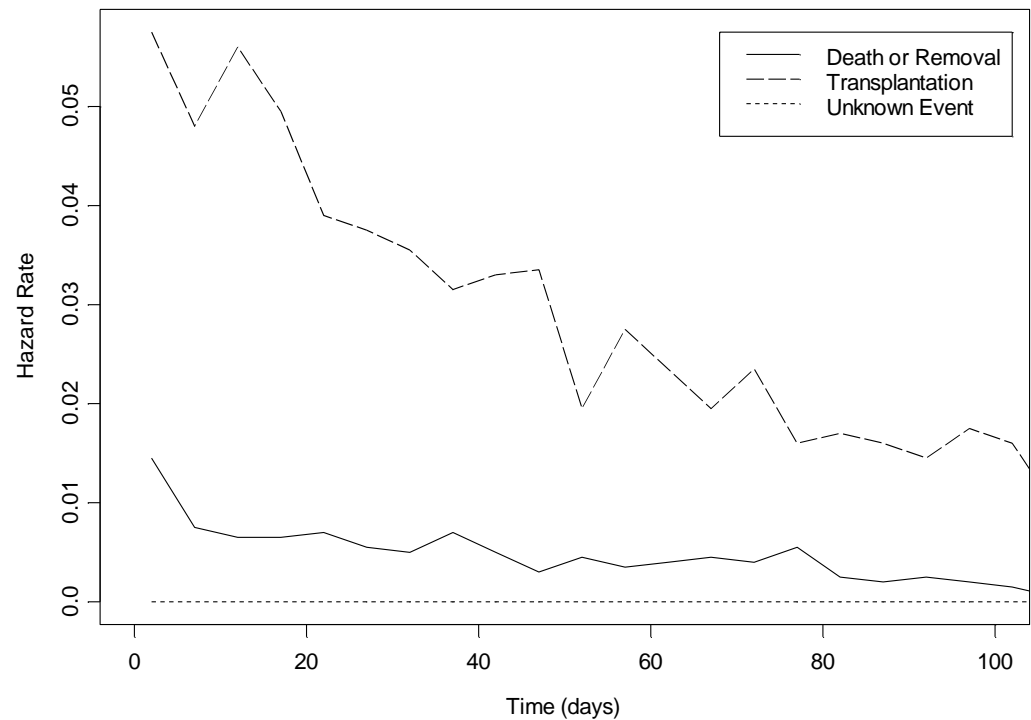


Figure 4.5 Hazard Rates for all outcomes from the waiting list for patients waiting for a routine transplant.

Log Cumulative Hazard plots (Appendix J, Sections J.1 and J.1.3) confirm that the times to death or removal from the waiting list of routine patients satisfy the PHs assumption. The Cumulative Hazard plot (Appendix J, Section J.1.2) confirms that an AFT model would be more appropriate for capturing the survival times of the super urgent patients. The plots by outcome (Appendix J, Section J.1.6) confirm that an AFT CR model would be appropriate for modelling the times to death or removal, and to transplantation.

Different parametric versions of the survival and competing risks models were next developed, and following goodness-of-fit analysis the most appropriate models were identified. The two most appropriate models were:

(1) Survival Models:

- A log-logistic survival (AFT) model to capture the times to death or removal censored at all other events for patients requiring a super urgent transplant;
- A Weibull (PH) model stratified by first transplant or not, to capture the times to death or removal censored at all other events for patients requiring a routine transplant.

(2) Competing Risks Model:

- A Weibull model (re-parameterised as AFT) stratified by first transplant or not, to capture the events death or removal, and transplantation censored at all other events.

The model development processes are summarised in Appendix J, and the goodness-of-fit analyses (plots of the Kaplan-Meier Estimates and the Weibull curves) conclude that the competing risks model captures the death or removal event more closely.

Figures 4.6-4.7 show the overall fit of the competing risks Weibull model (for simplicity a null model is presented here), which was identified as the most appropriate from the goodness-of-fit analysis performed (Appendix J), and will be used within Hepatica. It is interesting to see the shape of the fitted curves, however, we can not expect the same shape as the initial Kaplan-Meier curves, since the null model would represent an “average” person and the older patients may pull the curve down unrealistically. Also, few actual deaths or removals will be recorded for the longer times (due to patients lost to follow-up etc.) and so the Kaplan-Meier curve will have larger confidence intervals (i.e., more uncertainty to the tail end of the graphs shown).

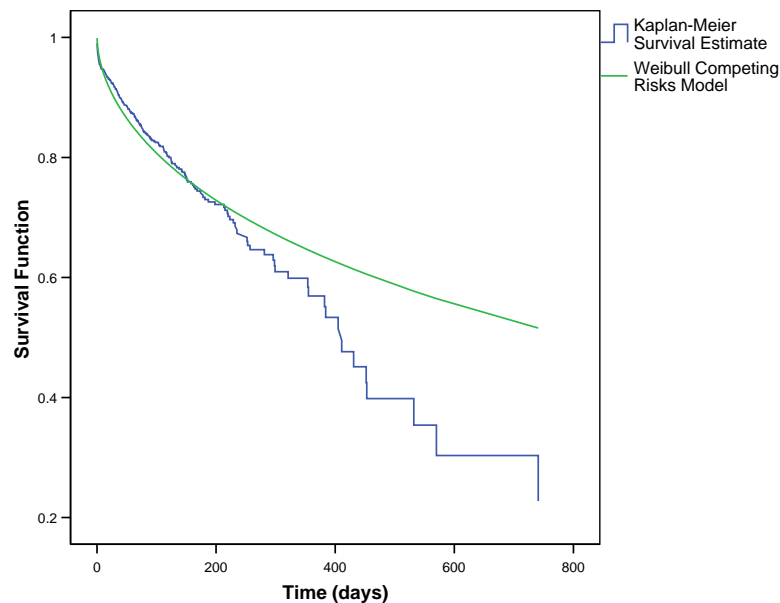


Figure 4.6 Weibull Competing Risks null model and Kaplan-Meier Estimate for the event Death or Removal for patients awaiting their first transplants.

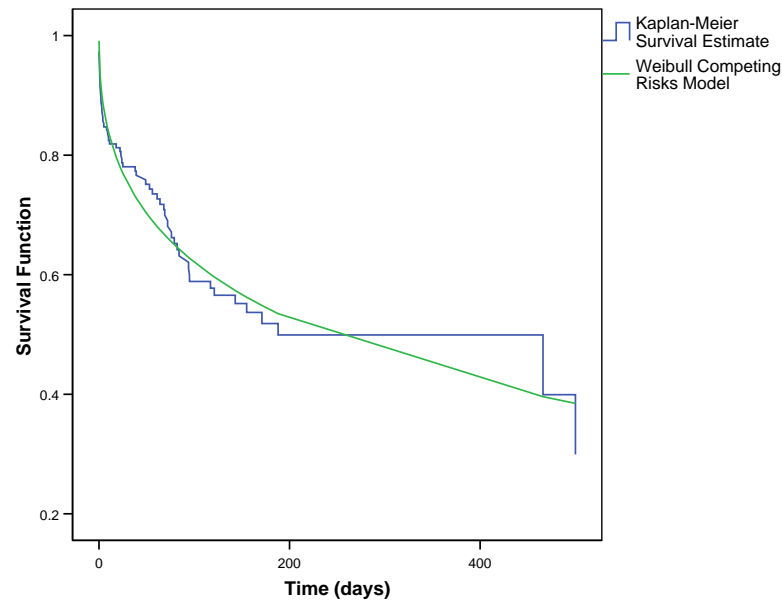


Figure 4.7 Weibull Competing Risks null model and Kaplan-Meier Estimate for the event Death or Removal for patients awaiting their successive transplants.

4.4.2 Final Model

The Weibull competing risks model developed (Appendix J) captures the times to the outcomes, death or removal, and transplantation, from the point that the patient joins the waiting list. However, it will only be required to estimate the times to death or removal within Hepatica, the decision about when to transplant a patient will be dependent on the allocation rules in place (as explained in Section 4.4.1). From Figures 4.6 and 4.7 it can be seen that the competing risks model (which takes no account of explanatory variables) provides a reasonable approximation to the observed data (Kaplan-Meier Estimate), especially within the early days, when most of the events occur.

The times estimated using the models will have no upper bound so in order to make them more realistic, when applying this sub-model to Hepatica, the estimated death or removal times will be truncated at 730 days from joining the

waiting list for patients requiring a routine transplant and 60 days from joining the waiting list for patients requiring a super urgent transplant. Additionally, all patients progressing through the model are given a maximum life expectancy of 95 years. This constraint is more significant when determining post-transplant survival times (see Section 4.5.2) but could be of relevance for patients being re-listed onto the waiting list.

The formulae which will be used in generating the death or removal times (Equations (4.3) and (4.4)) are based on the general formula of the p^{th} percentile value for the i^{th} individual, for the Weibull model:

$$t_i(p) = \exp \left[\sigma \log \left\{ -\log \left(\frac{100-p}{100} \right) \right\} + \mu + \underline{\alpha}' \underline{x}_i \right] \quad (4.2)$$

where $t_i(p)$ is the length of time after joining the waiting list that patient i will experience death or removal,

p is the percentile value,

$$\sigma = \frac{1}{\text{shape}},$$

$$\text{scale} = \exp \left(\frac{-\mu}{\sigma} \right),$$

μ is the mean,

$\underline{\alpha}$ is a vector of coefficients of the explanatory variables,

\underline{x}_i is a vector of the explanatory variables for the i^{th} individual.

Hence, the model fitted in Appendix J gives the following two equations ((4.3) and (4.4)) for generating the times to death or removal.

For patients joining the waiting list for their first liver transplant:

$$t_i(p) = \max \left(95 \times 365 - Age_i, f(txurg) \exp \left[1.27 \log \left\{ -\log \left(\frac{100-p}{100} \right) \right\} + 8.06 + \underline{\alpha}' \underline{x}_i \right] \right) \quad (4.3)$$

$$\text{where } \underline{\alpha} = \begin{pmatrix} -0.27 \\ 0.30 \\ 0.09 \\ -0.02 \\ -0.17 \\ -4.27 \\ 0.63 \\ -0.45 \\ 0.52 \\ -0.18 \\ -1.36 \end{pmatrix} \text{ and } \underline{x}_i = \begin{pmatrix} B_i \\ C_i \\ E_i \\ Age_i \\ Gender_i \\ Urgency_i \\ Disease1_i \\ Disease3_i \\ Disease5_i \\ Disease8_i \\ Disease12_i \end{pmatrix} \text{ within the developed model, and}$$

$$f(txurg) = \begin{cases} 60, & \text{if the patient requires a super urgent transplant} \\ 730, & \text{if the patient requires a routine transplant} \end{cases}$$

where $f(txurg)$ represents the cut-off times for different urgencies of transplant.

Table 4.10 details the explanatory variables in vector \underline{x}_i .

For patients joining the waiting list for their successive liver transplants:

$$t_i(p) = \max \left(95 \times 365 - Age_i, f(txurg) \exp \left[1.61 \log \left\{ -\log \left(\frac{100-p}{100} \right) \right\} + 8.04 + \underline{\alpha}' \underline{x}_i \right] \right) \quad (4.4)$$

where the variables are as before.

Table 4.10 Explanatory Variables of the Weibull Competing Risks Waiting List Outcome Model.

Explanatory Variables	Corresponding Patient Characteristic
B_i	1 if patient is from Centre B 0 if patient is not from Centre B
C_i	1 if patient is from Centre C 0 if patient is not from Centre C
E_i	1 if patient is from Centre E 0 if patient is not from Centre E
Age_i	Patient age in days, at registration on to the waiting list
$Gender_i$	1 if a male patient 0 if a female patient
$Urgency_i$	1 if requiring a super urgent transplant 0 if requiring a routine transplant
Patient's $Disease1_i$	1 if patients primary liver disease is either primary biliary cirrhosis, autoimmune cirrhosis, or secondary biliary cirrhosis 0 if a different primary liver disease
Patient's $Disease3_i$	1 if patients primary liver disease is related to cancer 0 if a different primary liver disease
Patient's $Disease5_i$	1 if patients primary liver disease is diagnosed but falls into the “other” category 0 if a different primary liver disease
Patient's $Disease8_i$	1 if patients primary liver disease is Hepatitis B 0 if a different primary liver disease
Patient's $Disease12_i$	1 if patients primary liver disease was not reported 0 if a different primary liver disease

Equations (4.4) and (4.5) can be used to generate times by generating a random number for p between 0 and 99.

Interpretation and Evaluation of the Resultant Model

The explanatory variables B_i , $Urgency_i$, $Gender_i$, Patient's $Disease3_i$, Patient's $Disease8_i$, and Patient's $Disease12_i$ have negative coefficients. This indicates that if a patient falls into any one of these groups (i.e., from centre B, super urgent patient, male patient, patients with liver cancer, patients with

Hepatitis B, and patients with non reported liver disease), then the time to death or removal once joining the waiting list, is shorter (i.e., they are worse off) than for a patient who does not have any of these characteristics. Age_i also has a negative coefficient, which implies that the older the patient, the lower the pre-transplant life expectancy.

The explanatory variables which have positive coefficients are: C_i , E_i , Patient's $Disease1_i$, and Patient's $Disease5_i$ (i.e., from centre C, from centre E, patients with other cirrhotic diseases, and patients with other diagnosed disease), with patients from these groups the time between listing and death or removal is longer than for similar patients without these characteristics.

The model is realistic since, the very large negative coefficient for urgency captures that super urgent patients will survive for a much shorter period than routine patients. It also captures the effect of older patients surviving for a shorter period of time on the waiting list. Centre effects are also captured, which will reflect how the different centres interpret the assessment guidelines and the variation in the patient mix joining the waiting list from each of the centres.

This model will be used within Hepatica when a patient joins a waiting list. Within Hepatica a time will be sampled from the model to determine when the patient will experience death or removal from the waiting list (assuming that they do not receive a transplant in the meantime).

4.4.3 Overall Evaluation

The model which has been developed can be sampled from within Hepatica, using a formula to determine death or removal from once a patient has joined the waiting list. It allows for times to be generated for the whole range of liver diseases represented by patients that join the waiting list. This avoids the use of detailed, disease specific models which have been implemented in previous liver transplant matching models (Eldabi *et al.* 2001).

A CR approach allows for multiple events to be modelled simultaneously. This is useful when there are several possible outcomes, and when the outcomes which require censoring are not independent of one another. Here the time to transplantation and the time to unknown events, have different hazards (Figures 4.3 to 4.5) and so a CR approach is applicable.

Figures 4.6 and 4.7 show Kaplan-Meier plots with the null Weibull CR model curves. These look like reasonable approximations, however will never be identical, due to the cohort not representing an “average” person. The Kaplan-Meier estimate and estimated curve (as presented in Appendix J) show that the fit is reasonable.

4.5 Post-Transplant Outcome Model

4.5.1 Development

The next set of models to be developed aim to capture the outcomes experienced by the patients after they have been transplanted with a new liver. The possible outcomes which were considered after a patient receives a liver transplant were: graft failure, death and re-listing. The key requirement for Hepatica is to determine which outcome a patient will experience, and when, based on the characteristics of the patient, donor, and the transplant operation performed (as outlined in Section 3.7.2), and summarised in Table 4.11.

Many previous studies model the event of graft failure separately to death, however, once a patient's liver graft fails, they generally die within 24 hours. Within the observed data, 99.5% of patients to experience graft failure (but not re-listed), died within 24 hours and the remainder within 48 hours. Once a patient is re-listed onto the waiting list they are assumed to follow the outcomes as defined by the distributions developed in Section 4.4. Therefore, we are only interested in modelling the two outcomes post-transplantation of (1) re-listing and (2) death or graft failure. Since the majority of deaths which are observed within the data will ultimately be due to liver failure, the events death and graft failure can be combined and it is not required to distinguish if the deaths are due to other causes (Gunson 2004).

Table 4.11 Covariates considered for the Post-Transplant Outcome Model.

Variable	Appropriate Values	Discussion
Donor-Patient ABO match	Identical, Compatible, Incompatible (as defined in Section B.1, Appendix B).	Blood group match will influence early graft rejection.
Cold ischaemic time	> 12 hours or not.	The time a liver spends outside of a body will influence how the liver functions post-transplant.
Donor age	> 65 years or not.	Defines a characteristic of marginal livers, which are associated with shorter survival.
Donor cause of death	Donor cause of death groups outlined in Section A.2 (Appendix A).	Defines a characteristic of marginal livers, which are associated with shorter survival.
Transplant Number	First, Successive.	The transplant number will influence both the severity of illness and issues such as recurring diseases.
Completeness of liver used	Whole, Reduced, Split.	Defines a characteristic of marginal livers, which are associated with shorter survival.
Primary liver disease at registration	Disease groups as outlined in Section A.1.2 (Appendix A).	Certain liver disease will have a greater chance to recurring post transplant.
Patient Age at transplant	Age in days.	Older patients may suffer from illnesses other than liver disease.
Recipient/Donor rhesus match	Match, No Match.	Rhesus match is known to effect other post-organ transplant survival.
Transplant Urgency	Routine, Super Urgent.	The severity of illness before the transplant may influence how likely a patient is to recover from the operation.
MELD score	Both as a continuous value based on the original score, and as a factor variable as explained in A.3 (Appendix A).	The severity of illness before the transplant may influence how likely a patient is to recover from the operation.
Donor gender to Recipient Gender	4 groups: male to male, male to female, female to male, female to female.	Gender may influence the size and weight of an organ which may affect the overall outcome experienced.
Donor weight minus Patient weight	Continuous variable.	Weight matching is considered important in the current system.
Patient Body Mass Index	Factor variable as defined in Section A.4 (Appendix A).	Body mass index may influence the ability of recovering from the transplant.
Patient Gender	Male, Female.	The prognosis for many diseases varies by gender.

Information about transplant operations and the outcomes of patients post-transplant is kept by UK Transplant, and was obtained from them for this analysis (Section 3.7.1). However, some outcomes will not be reported, as the patients will eventually go back to just seeing their general practitioners, who will monitor progress themselves.

The dependent variables for this analysis were the outcomes experienced and the time at which these outcomes occur. The independent variables (listed in Table 4.11) considered were identified as potentially influencing the possible outcomes post-transplant, and included patient and donor attributes and MELD score which is based on clinical measures. MELD score may influence the post-transplant outcomes a patient experiences, since it can determine the severity of a patient's illness and justify a decision to re-list or not.

Model Development

Basic descriptive analyses were utilised in identifying which distributions the various attributes took (e.g., shape of age/weight distributions).

Figure 4.8 depicts the hazard rate curves (as defined in Equation (2.8)) for the events: (1) to re-listing, (2) to death or graft failure, and (3) to unknown eventual outcomes, post-transplantation. It confirms that the hazard rate curves for the events re-listing, death or graft failure, and unknown events are different from one another (i.e., not independent of cause), and that the competing risks modelling approach may be more applicable.

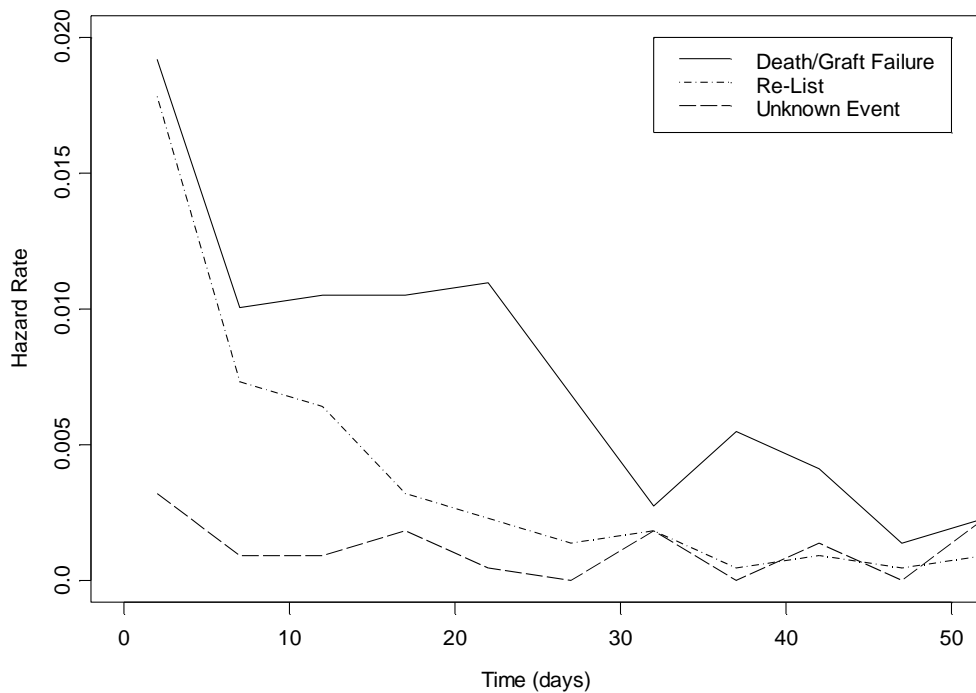


Figure 4.8 Hazard Rates for all the outcomes post-transplantation for all patients.

However, as for pre-transplant, both types of models (a survival model and a competing risks model) will be developed. The survival model will consider the outcome death, graft failure, or re-list censored at unknown events. While the competing risks model will consider the two outcomes death or graft failure, and re-listing censored at unknown outcomes. From the methodology outlined in Sections 3.6.3 [A] and under the competing risks model development process section (and presented in Appendix K), it was determined that the log-logistic survival model which considered the event death, graft failure, or re-list censored at all other events, was the most appropriate for capturing the post-transplant outcomes.

The competing risks modelling approach was found not to be applicable for the post-transplant outcomes, since the basic assumptions, of PH or AFT under competing risks, did not hold. This is shown by the lines crossing in the plots of Log Cumulative Hazard by outcome (Appendix K Section K.1.5 Figure K.4) and Cumulative Hazard by outcome (Appendix K Section K.1.6 Figure K.5).

Figure 4.9 shows that the overall fit of the null log-logistic survival model developed, with the Kaplan-Meier survival estimate.

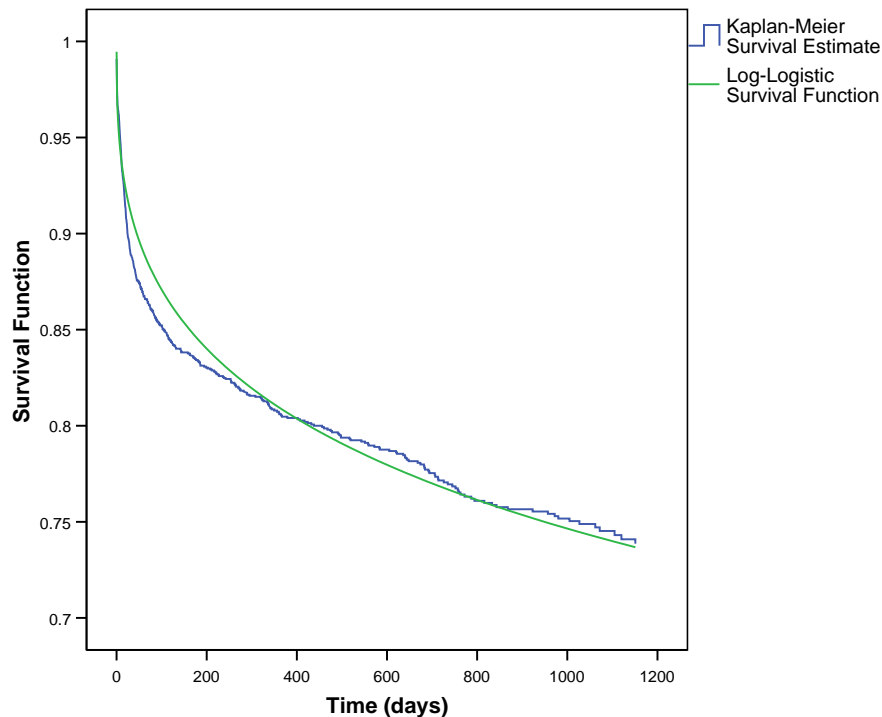


Figure 4.9 Log-Logistic null survival model and Kaplan-Meier Estimate for the event Death/Graft Failure and Re-Listing post-transplant.

4.5.2 Final Model

The developed log-logistic survival model (Appendix K) captures the time to the outcomes death/graft failure or re-listing, from transplantation. Figure 4.9

indicates that the null log-logistic model provides a reasonable fit to the observed survival Kaplan-Meier Estimate. In order to ensure that realistic survival times are estimated, it will be assumed that patients will only live until they are 95 years old, and so the related survival times will be cut accordingly.

For the log-logistic survival model, the p^{th} percentile value for the i^{th} individual is:

$$t_i(p) = \exp \left\{ \sigma \log \left(\frac{p}{100-p} \right) + \mu + \underline{\alpha}' \underline{x}_i \right\} \quad (4.5)$$

where $t_i(p)$ is the length of time after joining the waiting list that patient i will

experience death or removal,

p is the percentile value,

$$\theta = \frac{-\mu}{\sigma},$$

$$\kappa = \frac{1}{\sigma},$$

θ and κ represent the log logistic distribution parameters,

μ is the mean,

$\underline{\alpha}$ is a vector of coefficients of the explanatory variables,

\underline{x}_i is a vector of the explanatory variables for the i^{th} individual.

This formula can be used to generate a death/graft failure/re-list time for the patients who have been transplanted. The model fitted in Appendix K gives the following equation for generating these times:

$$t_i(p) = \max \left(95 \times 365 - PAge_i, \exp \left\{ 2.57 \log \left(\frac{p}{100-p} \right) + 9.15 + \underline{\alpha}' \underline{x}_i \right\} \right) \quad (4.6)$$

where the variables are as before and where

$$\underline{\alpha} = \begin{pmatrix} 1.85 \\ -1.05 \\ -2.48 \\ -0.03 \\ -1.01 \\ -0.04 \\ 0.89 \\ -1.50 \\ -2.39 \\ 1.33 \\ 1.29 \end{pmatrix} \quad \text{and} \quad \underline{x}_i = \begin{pmatrix} Whole_i \\ DAge_i \\ Dcod5_i \\ (DWeight - PWeight)_i \\ Meld3_i \\ PAge_i \\ Disease1_i \\ Disease5_i \\ Disease6_i \\ Disease10_i \\ Identical_i \end{pmatrix} \quad \text{within developed model.}$$

Table 4.12 details the explanatory variables in vector \underline{x}_i .

Equation (4.6) can be used to generate times from transplantation to a post-transplant outcome by generating a random number for p between 0 and 99.

Interpretation and Evaluation of the Resultant Model

The log-logistic survival curve implies that the hazard just after transplantation increases and then starts to decrease. The risk of re-listing or death/graft failure is greatest straight after a transplant as this is when the immune system may reject a graft. After this time the risk diminishes.

Table 4.12 Explanatory Variables of the Log-Logistic Survival for the Post-Transplant Outcome Model.

Explanatory Variables	Corresponding Patient, Donor, or Transplant Characteristic
$Whole_i$	1 if the patient was transplanted with a whole liver 0 if the patient was not transplanted with a whole liver
$DAge_i$	1 if the liver came from a donor aged over 65 years 0 if the donor was less than 65 years old
$Dcod5_i$	1 the donor died due to an infection 0 the donor did not die due to an infection
$(DWeight - PWeight)_i$	The difference between the donor weight and patient weight
$Meld3_i$	1 if MELD score at the time of transplant is in group 3 0 if MELD score in another group
$PAge_i$	Patient age at the time of the transplant
$Disease4_i$	1 if patient's primary liver disease is either primary biliary cirrhosis, autoimmune cirrhosis, or secondary biliary cirrhosis 0 if a different primary liver disease
$Disease5_i$	1 if patient's primary liver disease is diagnosed but falls into the "other" category 0 if a different primary liver disease
$Disease6_i$	1 if patient's primary liver disease falls in the super urgent/acute disease group 0 if primary liver disease does not fall in to the super urgent/acute disease group
$Disease10_i$	1 if patient's primary liver disease is alcoholic liver disease 0 if primary liver disease is not alcoholic liver disease
$Identical_i$	1 if the patient's blood group was identical to the donors blood group 0 if blood groups were different

The explanatory variables $DAge_i$, $Dcod5_i$, $Meld3_i$, $Disease5_i$, and $Disease6_i$ have negative coefficients. This indicates that if a patient or their transplantation characteristics fall into any one of these groups, then the time from transplantation to death/graft failure or re-listing is shorter than for a patient who does not fall into any of these groups. $PAge_i$ also has a negative coefficient, which implies a reduction in the time to death/graft failure or re-listing from transplantation, for older patients. A patient aged 10 years older than another

with the same characteristics will progress along the survival curve 1.45 times faster (based on the acceleration factor $\phi^{-1} = \exp(-\underline{\alpha}'\underline{x}_i) = \exp(-0.0373 \times 10)$).

The explanatory variables which have positive coefficients are: $Whole_i$, $Disease1_i$, $Disease0_i$, and $Identical_i$, indicating that patients from these groups, experience a longer time between transplantation and Death/Graft Failure or Re-Listing, than similar patients who do not have these characteristics.

The model seems realistic as it identifies that characteristics associated with marginal livers (donor age, donor cause of death, non-whole), significantly reduce the time to a post-transplant outcome. As expected, it also identifies that as patient age increases the time to post-transplant outcome decreases. The model also captures that identically matched blood groups give rise to longer times to post-transplant events. This is realistic since patients with identically blood-matched livers are less likely to experience early graft rejection.

4.5.3 Overall Evaluation

The model which has been developed provides a formula which is easy to implement in the sampling of Death/Graft Failure or Re-Listing times, from once a patient has received a liver transplant. It allows for times to be generated for the whole range of liver diseases represented by patients that join the waiting

list. This avoids the use of detailed, disease specific models which have been implemented in previous liver transplant matching models (Eldabi *et al.* 2001).

The log-logistic model developed also allows capture of the higher initial risk, soon after transplant, through the use of a non-monotonic hazard function.

Figure 4.9 show Kaplan-Meier plots with the null log-logistic survival model curve. This looks like a reasonable approximation, however it will never be identical, due to the cohort not representing an “average” person. The Cox-Snell residuals (as presented in Appendix K) determine how well the model fits and Figure K.7 shows that the fit is reasonable.

4.5.4 Further Validation

A recent study (Barber *et al.* 2007) considered the survival of adult patients (patients aged 17 years or older at the time of transplantation) who had been transplanted with a new liver, in the UK, between 1 January 1985 and 31 December 2003. Barber *et al.* (2007) developed a parametric AFT model with an underlying Weibull distribution for the survival times. Their calculations estimate that the median survival time of the liver allograft recipients was 22.2 years (95% confidence interval 19.3-25.6 years).

Using the post-transplant outcome model, summarised in Section 4.5.2, a similar calculation was performed. The log-logistic survival model was used to calculate median survival times (time to either death, graft failure, or RL) for the

patients observed to have been transplanted in the UK after joining the waiting list between 1 January 1999 and 31 December 2002, by 6 October 2003. An average of the median times was then calculated and this estimated that liver transplantation lengthens the life of a patient suffering from ESLD by 19.7 years. This estimate falls within the confidence limit which Barber *et al.* (2007) have estimated and is comparable to their result, when taking into account some inherent differences between calculations and study populations:

- (1) Barber *et al.* (2007) only estimate the survival benefits gained by patients who have survived for at least 6 months post-transplant, whereas our calculation considers all the transplanted patients; and
- (2) The mix of patients in both studies is slightly different to one another, as Barber *et al.* (2007) consider a proportion of patients transplanted between 1 January 1985 and 31 December 2003, whereas we consider the patients who joined the waiting list between 1 January 1999 and 31 December 2002 and who were transplanted by 6 October 2003.

4.6 Patient and Donor Arrivals and Assignment of

Characteristics

4.6.1 Arrival Rates

After initial checks for erroneous data, Stat::fit (an add-in available to run within the software package Simul8 which statically fits data to the most useful analytical distribution (Stat::fit is developed by GEERMS)) was used to fit distributions to the patient and donor arrivals. Stat::fit was used to determine

whether the arrival data resembled a Poisson process and hence decide whether the negative exponential distribution was appropriate for generating both patient and donor inter arrival times, (when interpreting the Chi-squared statistic, at the 99.9% level of significance). The arrival rates used within Hepatica were determined by the factors considered within Sections 3.3.1 and 3.3.2.

4.6.2 Assignment of Characteristics

When patients and donors arrive into the simulation model they are assigned characteristics which determine the patient to whom a liver transplant is allocated (based on the policy in place, as outlined in Section 3.3.4), and determine the patients' eventual outcome (as defined through the models in Sections 4.4 and 4.5). Therefore, the characteristics assigned are based on the information which is required for the allocation of the liver transplants and the information required in estimating survival times. Appendix L looks at the characteristics required and summarises any dependencies (e.g., a higher proportion of the Super Urgent/Acute disease group will require a super urgent transplant, than the other disease groups).

Table 4.13 Dependencies Found Between Characteristics to be Assigned.

	Dependencies Between
Patient Characteristics	Disease group and Transplant urgency Disease group and First transplant Disease group and Transplant centre Disease group and Patient gender Disease group and MELD group Transplant urgency and First transplant Transplant urgency and Patient gender Transplant urgency and MELD group First transplant and MELD group Transplant centre and MELD group Transplant centre and Blood group Patient weight and Patient gender
Donor Characteristics	Whole liver and Donor cause of death Whole liver and Transplant centre Donor cause of death and Transplant centre Donor age and Whole liver Donor age and Donor cause of death

The analysis reported several dependencies, which are summarised in Table 4.13.

4.7 Summary

This chapter summarised the development of the statistical sub-models which will be used within Hepatica, as well as explaining the main assumptions made. Statistical modelling techniques were employed, using a variety of software packages.

Three main models are developed, to capture outcomes from (1) assessment, (2) the waiting list, and (3) post-transplantation. Dependencies between attributes values were also tested for, to ensure correct assignments were made to the donors and the patients.

A logistic regression model captured the assessment decisions (of whether or not to list patients onto the waiting list) in one liver unit. The analysis found the following patient attributes significant in determining which patients are listed: transplant urgency, age, disease group, and MELD score. However, due to data limitations (as discussed in Section 4.3.3), this analysis led to a revision of the simulation model to be built and the simulation model will now not explicitly model the assessment phase.

A Weibull Competing Risks model captured the waiting outcomes (to death or removal and to transplantation). The patient attributes which were significant in predicting the time to an outcome from the waiting list, are: liver transplant number, centre, age, gender, transplant urgency, and disease group. The competing risks model was found to be more accurate than a survival model, as it can explicitly model the outcome of transplantation while the survival model would have to censor these times.

A log-logistic Survival model captured the post-transplant outcomes (to death, graft failure, or re-list). The attributes found to be significant are: transplant urgency, disease group, patient age, MELD group 3, donor weight minus patient weight, and attributes which describe a marginal liver (whole, donor age greater than 65 years, and donor cause of death due to infection). The log-logistic model indicates that there is a higher initial risk of death, graft failure, or re-list, which would be expected as the patient's body adjusts to the new liver, and

immunosuppression treatment. The post-transplant model has been validated using the results from a recently published study (Barber *et al.* 2007).

Overall interpretation of the sub-models suggested that as patient age increases, patients are less likely to be transplanted and more likely to die, or if transplanted, to experience graft failure or death quicker. This could be since patients are less likely to be listed or allocated a transplant if they are older and also that older patients often suffer from more complications than younger patients.

Chapter 5

Simulation Design, Verification and Validation

5.1 Introduction

This chapter details the various assumptions that have been made when designing and implementing the simulation experiments and explains why these assumptions are valid. The chapter reports the analysis performed in verifying and validating the base model. Verification is required in order to check that Hepatica has been coded correctly and is discussed in Section 5.4. Validation is necessary in order to establish if Hepatica is an accurate representation of the real system, and is reported on in Section 5.6.

5.2 Simulation Design

This section describes the decisions made in designing the simulation experiments, including the length of the warm-up period, and the number of runs (replications) to be analysed for each scenario. The analysis which supports the decisions made is based on the base scenario as described in Section 5.3.

5.2.1 A Terminating or Non-Terminating System?

The liver transplant allocation system has been identified as a non-terminating system, since there is no time at which the waiting list is cleared, and since patient and donor arrivals follow Poisson arrival rates (so may arrive at any time of the day).

However, the number of patients within the system (or the total time the patients spend in the system) will not reach a steady state for a number of years, if at all. This is due to the increasing number of patients that could potentially be re-listed onto the waiting list, as more transplants take place (resulting in a greater stock of patients potentially requiring a re-transplant).

5.2.2 Simulation Initialisation & Determining the Warm Up Period

Cold systems can lead to biased results. There are three ways in which a non-terminating system may be “warmed up”:

- (1) Using starting conditions (by populating the activities and queues with patients recorded from the real system);
- (2) Using a warm up period (running the simulation model and not recording any results, until the model contains a realistic number of patients in each activity/queue); or
- (3) A combination of the above two approaches.

For this model both a warm-up period and the use of starting conditions are required. Data are easily obtained for the number of patients waiting for a transplant at any point in time. However, data relating to patients who received their transplants a few years ago, is not easily attainable. This is because a few years after the transplantation date a patient will no longer be seen by the liver unit and instead care will be provided by their local general practitioner. These patients may however require another transplant in the future and if they do, they will go back to the liver unit. Therefore, a warm-up period is required to obtain a stock of patients which can be re-listed on to the waiting list.

A warm-up period by itself is not adequate since the simulation would start with no patients on the waiting list. If very few patients are on the waiting list when a donor liver arrives, then the rules implemented may lead to unrealistic allocations. Also, a decision would be required as to when to start the arrival of donated livers, since if the donated livers arrived at the start when no patients were on the waiting list, this may mean that donated livers are initially wasted and the waiting list may never build up with a realistic number of patients.

After the base scenario model had been verified (as reported in Section 5.4), 20 replications were performed to identify a suitable duration for the warm-up period. Figure 5.1 confirms that the rate of increase in the proportion of patients who are on the waiting list and are waiting for their second or greater liver transplant, slows right down after around 730 days. Therefore, for all the analysis a warm-up of 3 years (1,095 days) will be used. This is in line with the

10% of patients who were joining the waiting list for their second or successive liver transplant between 1999 and 2002.

(Note: the percentage of patients waiting for a successive transplant is expected to increase for a number of years, as more patients will be transplanted and therefore potentially re-listed. In the real system this is controlled by the decisions made by the liver consultants).

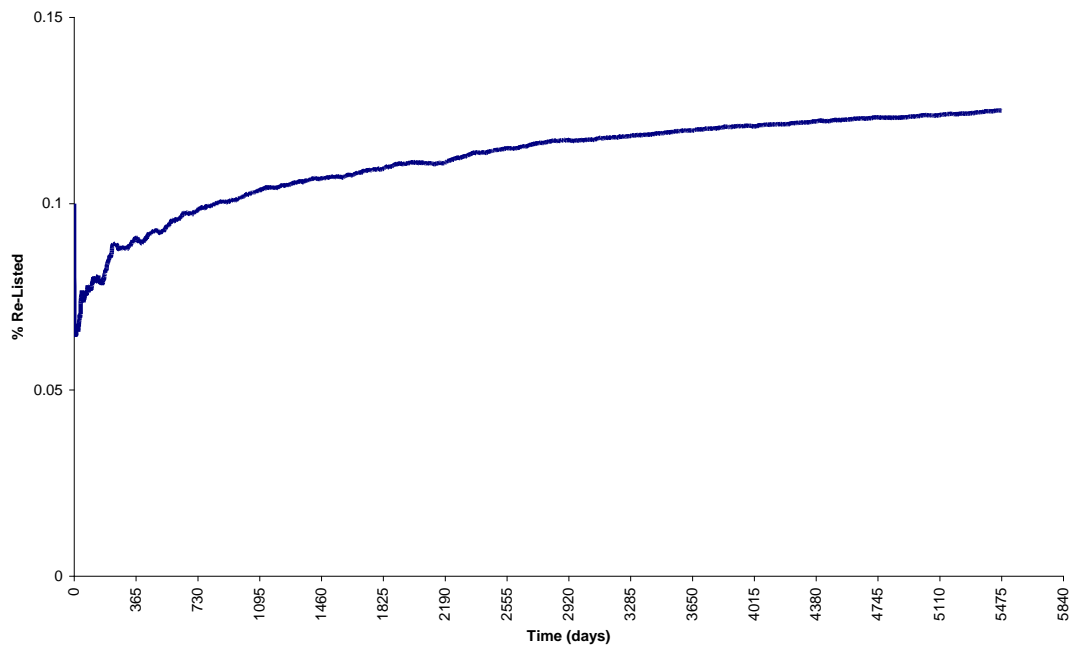


Figure 5.1 The percentage of re-listed patients on the waiting list.

It is important for the percentage of re-listed patients to be steady as this confirms that there are a steady stream of patients re-joining the waiting list, and that the system has “warmed-up”, enough. As noted previously, the system may never actually be truly stable (Section 5.2.1).

5.2.3 Number of Replications

The Confidence Interval Method was used to determine the number of replications required to obtain a 95% confidence in the value obtained for the mean time spent by patients on the waiting list (Robinson 2004).

The only time within Hepatica which is not sampled from a known distribution is the time from joining the waiting list to receiving a transplant. The times observed to death or removal from the waiting list will depend on whether a patient has received a transplant. So the mean time spent on the waiting list is an important value which Hepatica should seek to estimate accurately.

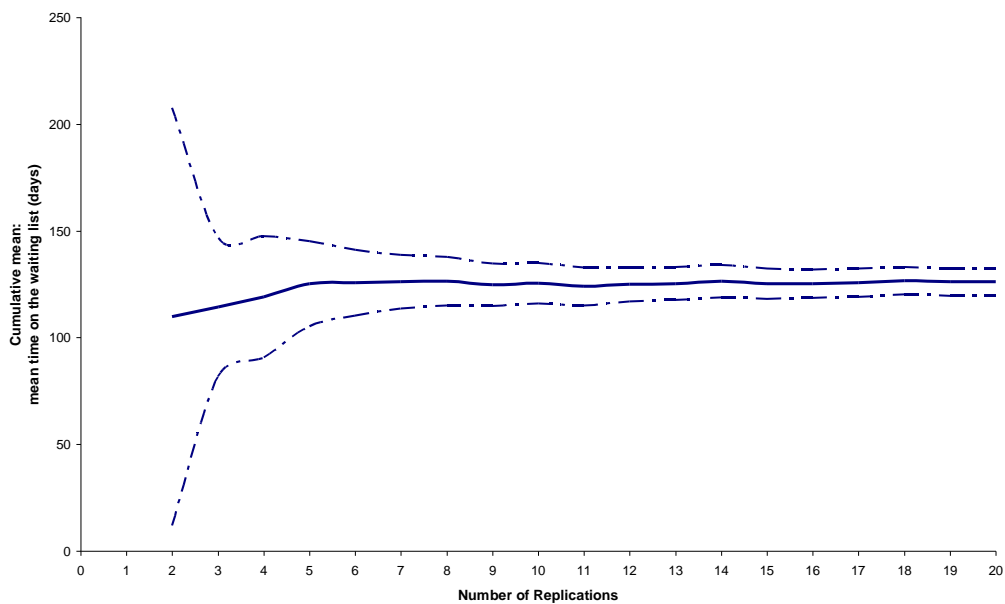


Figure 5.2 Determining the number of replications required (using the Confidence Interval Method).

From Figure 5.3 we can see that the overall mean time patients are on the waiting list levels off from about 7-8 replications. Most of the benefit is gained from 7-8 runs and additional replications do not reduce the size of the

confidence interval (CI) greatly, and the confidence interval is reasonably small (95% CI % deviation 9-10%). As a result of this analysis it was decided that 10 replications would be observed for each alternative scenario that was run – this caters for possible difference between scenarios.

5.2.4 Random Number Seeds

For experimentation purposes 10 sets¹¹ of random number seeds have been generated. These will be implemented in each of the scenarios considered. This will be done so that, as far as possible, we are comparing like for like between the scenarios (i.e., the same patient and donor arrival times and attributes will be generated across the particular demand and supply scenario).

5.3 Base Scenario

This chapter concentrates on the first base scenario, which implements the allocation rules in place at the time the data from UKT were gathered. It corresponds to the allocation rules L1 outlined in Section 3.3.4 and assumes a constant patient mix (A1 Section 3.3.3), a constant supply of liver donations (S1 Section 3.3.2), and a constant demand for liver transplants (D1 Section 3.3.1).

The activity flow diagram below (Figure 5.3) outlines the basic structure of Hepatica developed to capture the main outcomes experienced by patients that join the UK liver transplant waiting list. This outlines the flows considered

¹¹ Each set consists of six seeds, since this is the number required in Witness.

within the base scenario and the alternative scenarios (as outlined in Section 3.3).

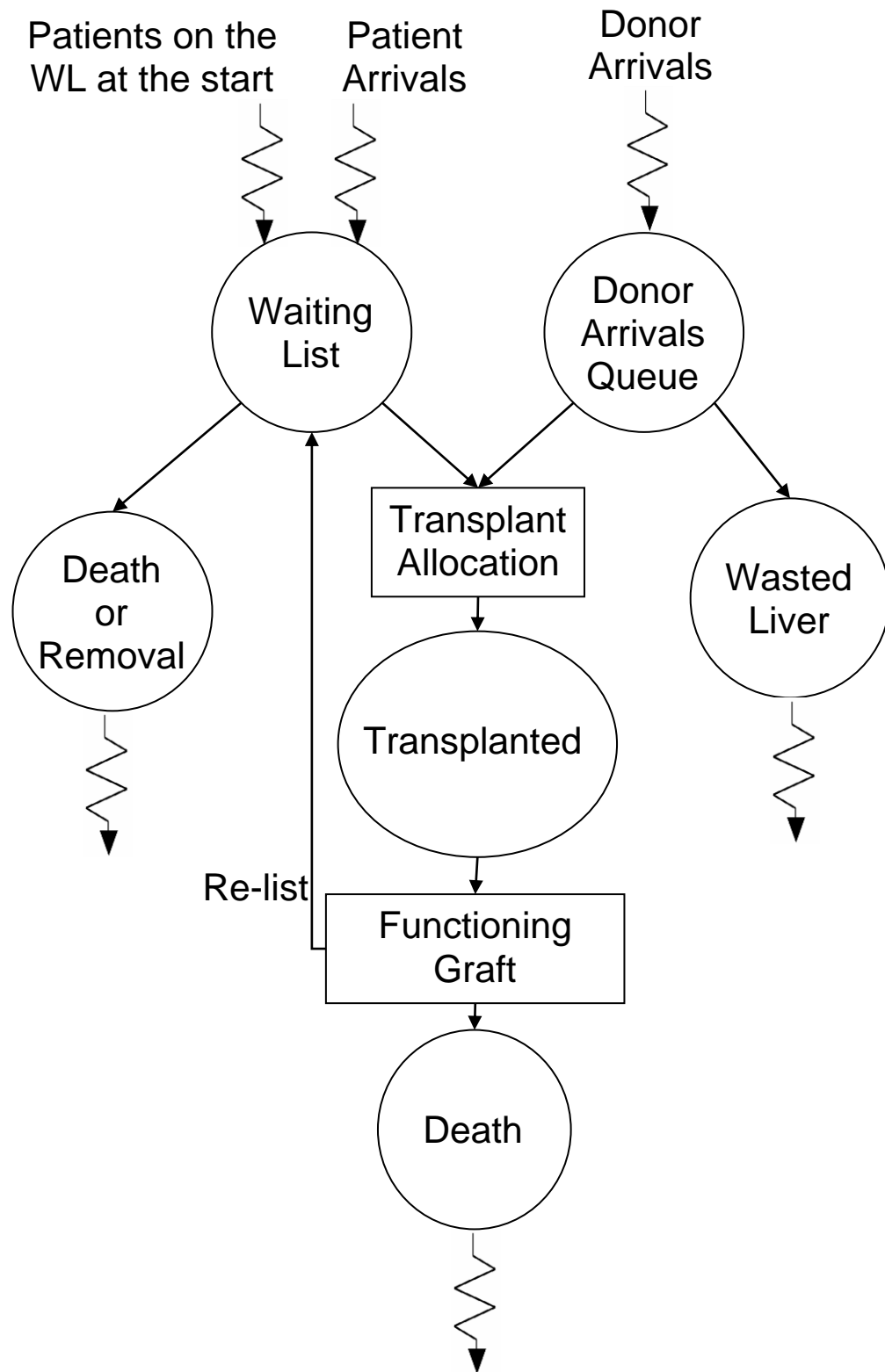


Figure 5.3 Activity Flow Diagram of Hepatica

Starting Conditions and Patient Arrivals on to the Waiting List

The simulation initially starts with 107 patients on the waiting list. This equates to the number of adult patients that were observed to be on the waiting list on 1st January 2003.

Once the patients arrive in the system they are directed straight on to the waiting list where they wait until either they receive a liver transplant (i.e., a donor is matched to a patient as described below) or until they reach the time of their death or removal. Patients experiencing this latter outcome are then directed out of the system via a dummy queue (which has been built in to help with data collection purposes) and are immediately taken out of the simulation.

Both starting patients and future patient arrivals have attributes that are assigned based on the overall distributions defined in Section 4.6 and each patient death or removal time is determined by sampling from the competing risk model (Section 4.4.2).

Arrivals of Donated Livers

The donor interarrival times were determined from the observed donor arrival rates as recorded by UKT. Their attributes were also determined from sampling from the distributions identified in Section 4.6. On the arrival of a donor, the matching algorithm determines if there is a suitable patient waiting on the waiting list (following the rule L1 in Section 3.3.4) and if a suitable patient exists then the patient and donor advance to the “Transplant Allocation” activity.

If there is no suitable patient within a day of the donor liver arriving then the donated liver is wasted and directed to the wasted liver queue. A donated liver which has been wasted spends zero time in the wasted liver queue (which exists for data collection purposes) and is then taken out of the simulation.

Transplant Allocation

The transplant allocation activity is the state in which a transplant takes place. This activity combines the donated liver and patient entities into a new “transplanted patient entity”, which retains the attributes of both the patient and the donor.

The transplant allocation activity takes zero time, after which the patient moves to a transplanted queue where they are allocated a death/graft failure/re-list time by sampling from the survival distribution (described in Section 4.4.2). An outcome flag is also created which determines which of these outcomes the patient will experience. The outcome flag is allocated at random, according to a set distribution, as no difference was found between the attributes of patients and the death/graft failure or re-list outcomes.

The patients are then directed to the functioning graft activity which routes them either back on to the waiting list queue (at the time of a re-list) or to the death or graft failure queue. The functioning graft activity takes zero time for patients who die and takes the amount of time to re-listing for the patients who are re-listed.

Re-Listing

The re-listed patients follow the same paths as the original patients (once they are placed back on the waiting list) and the following attributes are updated just before the patient leaves the functioning graft activity to be re-listed;

- (1) Liver transplant number is increased by one;
- (2) Patient age is recalculated; and
- (3) Disease group and urgency are updated to follow distributions observed for second or more transplants, as identified using UK Transplant data (Appendix L).

This base scenario has been verified and validated using the analysis described and reported in Sections 5.4 and 5.6.

5.3.1 Base Scenario - Model Runtime

The time taken to run one replication of the base scenario in Witness was roughly 5 minutes. The processor used was an Intel (R), Pentium (R) D CPU 2.80 GHz 2.79GHz, with 0.99 GB of RAM.

5.4 DES Base Model Verification

Several tests were performed during the development of the base scenario, to verify that the model was coded correctly. Comparisons were made between the output from the model and the assumptions that had been made in its development, as discussed in detail in Chapter 4. The checks were either

performed on one run (for verifying the simulation flows) of the base model or ten runs (for verifying the times generated), depending on the analysis required. Sections 5.4.1 to 5.4.7 give a detailed account of the verification checks that were performed for the base scenario. Additional checks were also performed to make sure that the aspects which were altered under the various alternative scenarios in Section 3.3, were also coded correctly and these are summarised in Section 5.5.

5.4.1 Calculation of Death/Removal and Death/Graft

Failure/Re-List times

Several times were determined within Hepatica and these were dependent on patient, donor and transplant attributes. These were the time to death or removal from the waiting list (which was based on the competing risk model developed in Section 4.4) and the time to death, graft failure or re-listing (which was determined using the survival model developed in Section 4.5).

The survival times were verified to check if the formulae for death/removal and death/graft failure/re-list times were accurately coded into Witness and a check was performed within Excel. The checks used the formulae as presented in Equations (4.3), (4.4) and (4.6); the value of p (where p is the percentile value) was determined at random using an in-built Witness function and this value, along with the relevant attributes, were output by Witness. Then a calculation was carried out to determine whether any of the times were incorrect. The

checks resulted in no difference being seen in any of the times generated by Witness and the times calculated using the formulae in Excel.

5.4.2 Distribution of Death/Removal times

The death/removal times were verified by plotting the cumulative distribution functions of the values assigned in Hepatica and those obtained from the null competing risk model (Section 4.4.1). Figure 5.4 shows that both distributions are similar. They will not be exactly the same as the “average” characteristics used in the competing risks model will not precisely resemble the sampled characteristics of all the patients in the simulation (as discussed in detail in Section 4.4.1).

From Figure 5.4 we can see that the cumulative distribution function of the times assigned are all within 730 days, this is because the model was coded to make sure that all the patients requiring a routine transplant, died within this time, in order to resemble the criteria for listing (Section 1.3.4). Also, the curve jumps at around 60 days - this will be due to the limit set on the time to death of patients awaiting super urgent transplants.

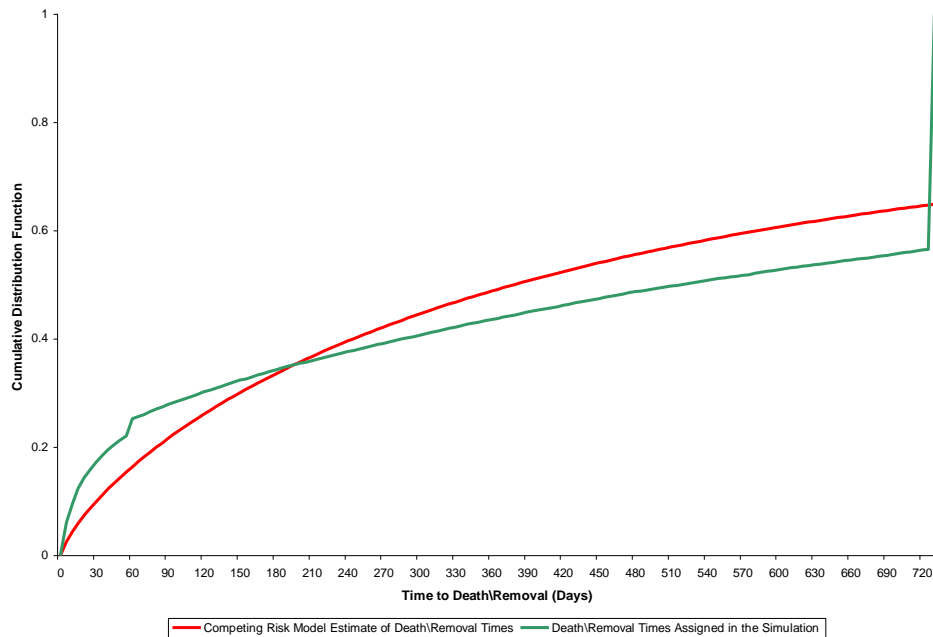


Figure 5.4 Comparison of the Death/Removal times assigned in the simulation and the Competing Risks null Model.

5.4.3 Realisation of Death/Removal and Death/Graft

Failure/Re-List times

Checks were performed to ensure that the patient outcomes experienced within Hepatica - of pre-transplant death or removal from the waiting list or post-transplant death, graft failure or re-listing - took place at the correct times. The information recorded from Hepatica included the time at which the event had occurred, the time at which the patient had joined the waiting list or had been transplanted (i.e., the times of origin, as listed in Section 2.4), and the length of time to the particular event (as generated by the distributions checked in Section 5.4.1). A calculation was then performed in Excel for each of the outcomes to check if the outcome had occurred at the correct time. No differences were found between the times the events occurred in the simulation and the times calculated in Excel.

5.4.4 Implementation of Allocation Rules

To verify the allocation rules in place, the simulation was run for 150 days with the following output from Witness:

- A list of all the patients registered on to the waiting list, the attributes of these patients, the time at which they joined the waiting list and the time at which they were scheduled to die or be removed from the waiting list;
- A list of all the donated livers with all donor attributes and the time at which they were donated; and
- A list of the transplanted patients with the associated donor and transplant attributes.

The list of donated livers was then checked, one by one. Each time a liver was donated, the waiting list was manually searched using the allocation criteria (for the base scenario this is based on patient and donor criteria as outlined in L1 Section 3.3.4) to find the appropriate patient to be transplanted. This information was then cross-checked to verify whether or not the correct patient had been transplanted within Hepatica. These checks found that the correct patients were being transplanted as according to the base scenario (L1) rules.

These checks also ensured that no transplants were being performed on patients who had already died, or been removed from the waiting list.

5.4.5 Updating Patient Ages

Patient age is updated at two stages within Hepatica. The death/removal time generated is dependent on the patient's age on registration to the waiting list, while the death/graft failure/re-listing time is dependent on the patient's age at the point they receive a transplant. In order for these times to be estimated accurately, the patient age must be updated before they can be generated. Therefore, the two stages at which the age is updated, are:

- (1) Once a patient is transplanted, and before they are allocated a post transplant outcome (so that the patient's age can be updated according to the length of time they were on the waiting list); and
- (2) Just before a patient is re-listed back onto the waiting list (so that the patient's age can be updated to incorporate the time between transplant and their eventual re-listing).

To check that the ages were being updated correctly two checks were performed. Once a patient has been transplanted, their old age (the age at which they joined the waiting list), their new age (at transplant) and the time between them joining the waiting list and their transplant were all output from Witness. Then using Excel a calculation was performed to determine whether the new age corresponded to the old age plus the time between them joining the waiting list and their transplant. The second check considered the patients just before they were placed back on to the waiting list. Here the output from Witness included the old age (the age at which the patient had been transplanted), the new age (at re-list), the time at which the patient had been transplanted, and the current time

(i.e., the time of re-list). Then in Excel a check was made to make sure that the new patient age equalled the old age plus the time between the transplant and re-listing.

Both of these verification checks concluded that the patient ages were being updated correctly.

5.4.6 Routing of Patients, Post Transplant

To check whether the patients were directed to the correct activities/queues after receiving a transplant, several files were output from Witness and analysed in Excel. One “overall” file was output from the “transplanted” queue listing all the patients that were transplanted with the post transplant outcome they were assigned (either death/graft failure or re-list).

For the patients who were re-listed another file which contained the post transplant outcome indicator and patient identification number was output. This file was compared to the overall file to check that the correct patients had been re-listed. A similar check was carried out to ensure that the correct patients experienced death/graft failure post-transplant.

All the checks confirmed that the patients were being re-listed or directed to death/graft failure correctly.

5.4.7 Routing of Wasted Livers

To check whether or not the livers that were not used for transplantation within one day after arriving into the simulated system were correctly counted as “wasted” livers, files containing information regarding the liver arrival time, the liver transplant time, the liver identification number and the liver wasted time were output from Witness. One run of the base scenario was then considered to check that all livers were used within a day of arriving. Since no livers are wasted in the base scenario, a dummy scenario which contained fewer patient arrivals was used to check if the livers were deemed wasted after a day of arriving. In Excel a calculation was made to find the differences between, firstly, the time the livers were used in transplants and the time at which they arrived, and, secondly, the time the livers were “wasted” and the time at which they arrived. The first check returned times which were all less than a day and the second returned times which were all equal to a day, so confirming that the model was correctly recording wasted livers.

5.5 Verification of Alternative Scenarios

The additional checks which were performed on the alternative scenarios, where the simulation factors were changed by one factor (demand, supply, assessment rule, or demand rule) are briefly described next. All the checks performed confirmed that the coding was correct for the various scenarios.

5.5.1 Alternative Demand Scenarios

The demand is altered as described in Section 3.3.1. To check that the demand factors were coded correctly, a yearly count for the number of patients arriving onto the waiting list and the list of these patients broken down by disease group was considered.

5.5.2 Alternative Supply Scenarios

The supply is altered as described in Section 3.3.2. To check that the correct numbers of donated livers were entering the system, an overall figure for the number of donations every year was considered.

5.5.3 Alternative Assessment Rules

The assessment rules are altered through changing patient prognosis as described in Section 3.3.3. To check if the prognosis without transplantation was either worse or better, a check similar to that outlined in Section 5.4.1 was performed, to make sure that the death/removal times were being calculated correctly within Hepatica.

5.5.4 Alternative Allocation Rules

For each set of allocation rules (as outlined in Section 3.3.4) the verification check outlined in Section 5.4.4 was performed, to make sure that the correct patients received a transplant.

5.6 DES Base Model Validation

Several tests were performed once the base scenario was verified to help validate the model against information contained within the UK Transplant data. The checks performed interpreted information from ten runs of the base model. Each run recorded data for a period of 1,460 days (4 years) with an initial period of warm up of 1,095 days (3 years). The models were run for 4 years for a number of reasons:

- (1) The data used from UK Transplant covered a 4 year period;
- (2) Four years should be long enough to demonstrate the effect of a changing the policy, demand, or supply; and
- (3) Four years is a realistic time period over which policies may last or be re-assessed after.

Sections 5.6.1 to 5.6.3 give the results obtained from the validation checks performed.

5.6.1 Time to Death/Removal

The times to death/removal from the waiting list observed in the base scenario were compared with those recorded within the UK Transplant dataset. Note that the death/removal times experienced by patients in Hepatica will be affected by both the simulated survival time and whatever allocation decisions were being made. For this reason it would not be surprising to see differences between UK Transplant and the simulation results.

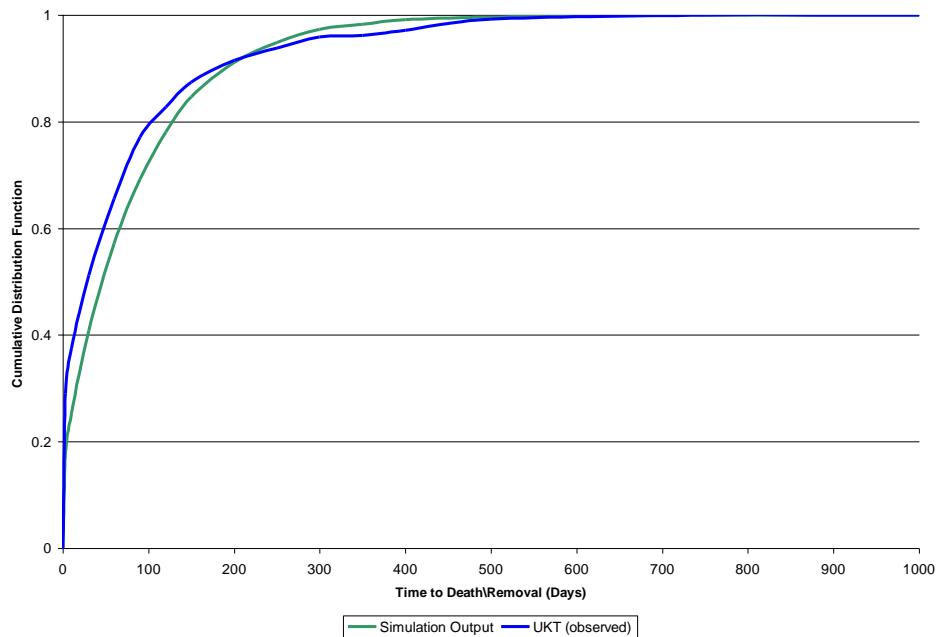


Figure 5.5 Comparison of the time to death/removal to occur in the simulation and the time to death/removal observed in the UKT data.

Figure 5.5 shows the cumulative distribution functions of the times to death/removal from the waiting list, as observed in the UK Transplant data and also within the base scenario simulation runs. The curves show that the distributions of times are similar, however the distribution observed within Hepatica shows that time times to death or removal were generally longer. This is the effect of more super urgent patients receiving transplants which leads to routine patients having to wait longer. This discrepancy is discussed further in Section 5.6.2.

5.6.2 Time to Transplant

The times to transplant from joining the waiting list observed in the base scenario were compared with those observed in the UK Transplant dataset. Note that the time to transplant experienced by patients in Hepatica is not explicitly

modelled, and is purely dependent on the allocation decisions were being made. Any differences observed could be caused by a variety of factors, rather than one specific element of the model.

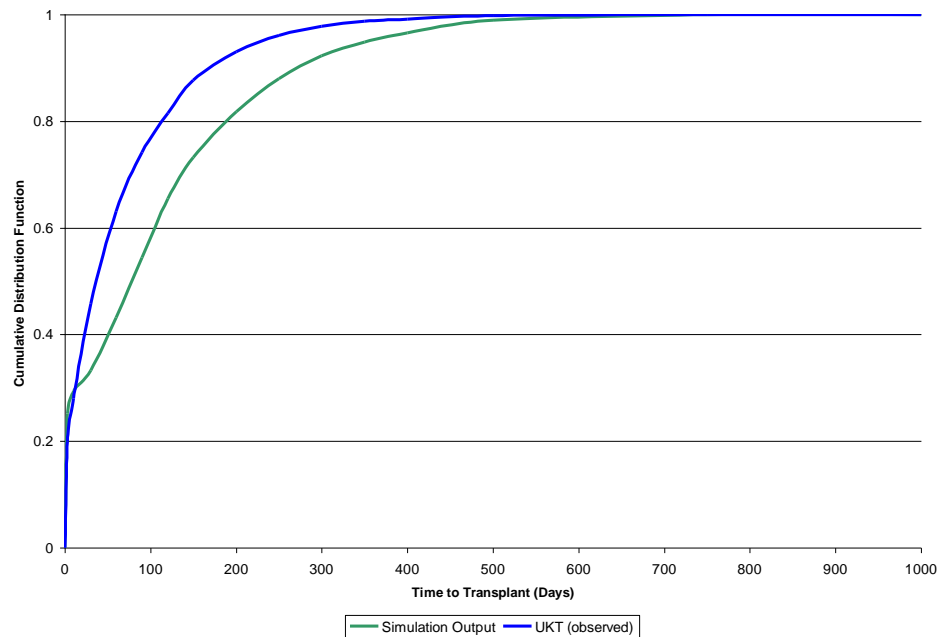


Figure 5.6 Comparison of the time to Transplant to occur in the simulation and the time to Transplant observed in the UKT data

Figure 5.6 presents the cumulative distribution function of the times to transplant from joining the waiting list as observed in the UK Transplant data and within the base scenario simulation runs. The curves are not identical; further investigation determined that this is because a greater proportion of super urgent patients are being transplanted within the simulation than observed in the UK Transplant data. Tables 5.1 and 5.2 indicate that roughly 10% more super urgent patients, and 4% fewer routine patients, received a transplant in the base case simulation.

Table 5.1 Observed and Simulated Outcomes from the Waiting List for Super Urgent Patients (UK Transplant 2004e).

Super Urgent Patients	UKT Data	Simulated
Transplanted (%)	76.8%	87.5%
Average Time to Transplant	3.2 days	1.2 days
Average Time to Death/Removal	4.7 days	1.2 days

Table 5.2 Observed and Simulated Outcomes from the Waiting List for Routine Patients (UK Transplant 2004e).

Routine Patients	UKT Data	Simulated
Transplanted (%)	85.7%	81.4%
Average Time to Transplant	78.6 days	163.6 days
Average Time to Death/Removal	89.7 days	96.6 days

In addition, the time to transplant for these super urgent patients is on average greater within the UK Transplant data (3.2 days), than within Hepatica (1.2 days). This indicates that super urgent patients are obtaining liver transplants quicker in the simulation, meaning that routine patients are having to wait longer for a transplant, often missing out completely. The discrepancy observed in Figure 5.6 demonstrates the net effect of this with routine patients (82% of all patients who join the waiting list) spending much longer on the waiting list before they are transplanted. At the start of the curve there is a sharper increase, which would represent the super urgent patients receiving transplants early on.

In Section 5.4.4 it was concluded that the allocation rules were being implemented correctly; so when a donated liver arrives into the system, this is being allocated according to the policy in place. The implication of this is that there is some key operational factor(s) regarding the transplant of super urgent patients which has not been documented in the literature or captured within

Hepatica. Further investigation would be required to resolve this, probably in consultation with clinicians, as discussed further in Section 7.5.3.

5.6.3 Time to Death/Graft Failure/Re-List

The times to death/graft failure/re-listing post transplantation as observed in the base scenario were compared with those observed in the UKT dataset. Note that the death/graft failure/re-listing times experienced by patients in Hepatica will be affected by both the simulated survival time and whatever allocation decisions were made. For this reason it would not be surprising to see differences between UKT and the simulation results.

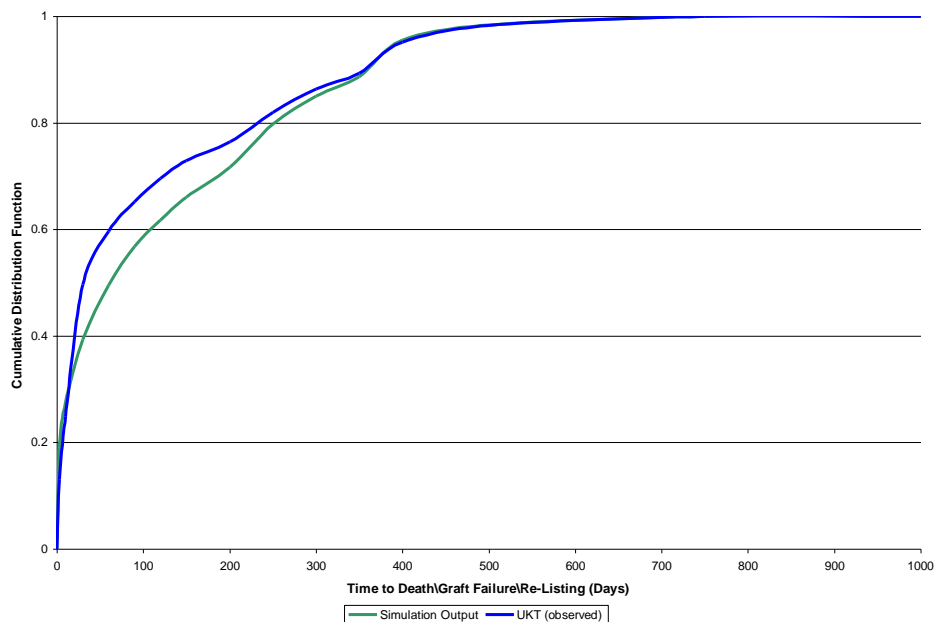


Figure 5.7 Comparison of the time to death/graft failure or re-listing to occur in the simulation and the time to death/graft failure or re-list observed in the UKT data

Figure 5.7 shows the cumulative distribution functions of the observed times to death/graft failure or re-list post-transplantation as observed in the UK Transplant data and within the base scenario simulation runs (i.e., the events that actually took place within the study observation period). Figure 5.8 displays the Kaplan-Meier Estimates for the times assigned to all transplanted patients within the simulation model and the times observed within the UK Transplant data set. The two curves are very similar, indicating that the survival model is suitable to use. The discrepancy after 3 years (1,095 days) results from fewer events being observed after this length of time, within the UK Transplant data. This would be due to issues, such as, patients being lost to follow-up.

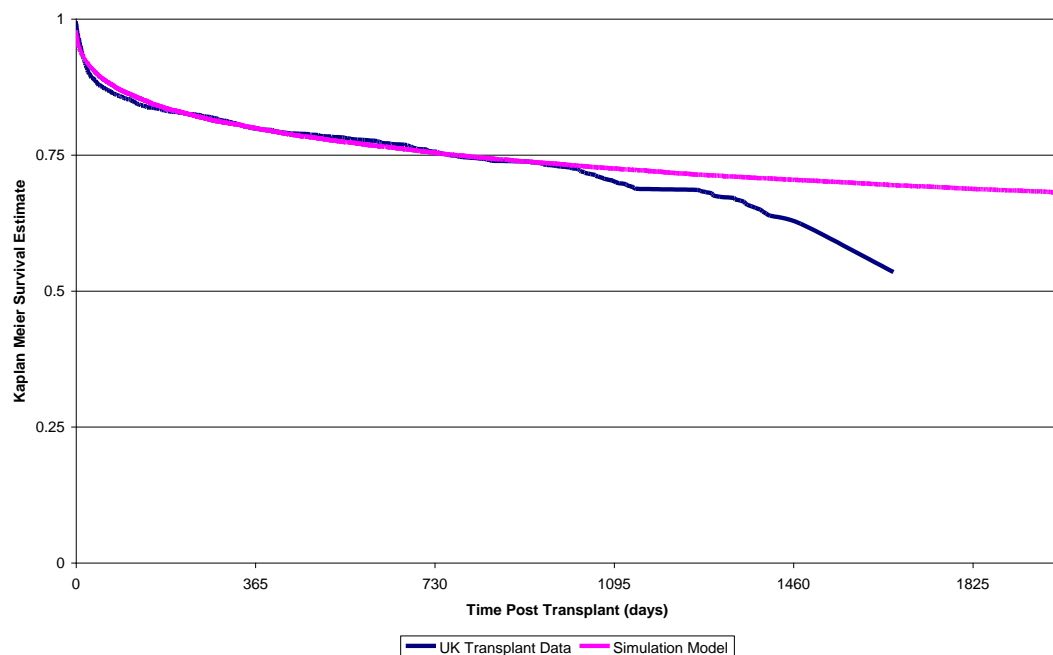


Figure 5.8 Kaplan-Meier Estimates for the Post Transplant Outcome Times

5.7 Summary

This chapter outlined the basic experimental set-up required. It determined that a 3 year (1,095 day) warm up period is necessary, and that 10 replications lead to a reasonable confidence in the accuracy of the results.

Also reported are the overall the verification and validation tests which confirm that the simulation model developed is a good representation (is both coded correctly and provides an accurate representation of the UK liver transplant system) to what is observed within the UK Transplant dataset.

Hepatica was found to allocate transplants to a higher proportion of patients requiring a super urgent transplant, and this may bias any results obtained using this model. It is likely that some aspect of the process of allocating transplants to super urgent patients has not been modelled fully, and requires further analysis. However, the experimentation carried out using the model (and presented in Chapter 6) is still valid, since relative comparisons are made between the various scenarios, all of which are influenced by this effect.

Chapter 6

Experimentation

6.1 Introduction

This chapter reports the results from running various scenarios in Hepatica. It starts by detailing the base scenario, equity measures, and utility measures used in comparing the various scenarios.

The scenarios considered are based on the experimental design explained in Section 3.7. The main findings from the analyses are summarised, with several key aspects are discussed, which require considering when/if the policies are changed.

6.2 Set Up of Experiments

6.2.1 Base Scenario

Two base scenarios were developed. The first scenario (B1) (as described in Section 5.3) was used for validation purposes and implemented the allocation rules in place at the time the data was collected. The second scenario (B2) uses the updated allocation rules (introduced in July 2006), with which all experimental scenarios are compared. The only difference between the two

scenarios is that B1 implements the allocation rules L1, while B2 implements the allocation rules L2. The main difference between the two allocation rules and the reasons for this are explained in detail in Section 3.4.4.

The base scenario (B2) assumes the allocation rules L2, a constant demand through time D1, a constant supply through time S1, and a similar patient mix joining the waiting list as between 1999-2002 A1 (all these factors are discussed in more detail in Section 3.3). All the scenarios simulated were run for a period of 7 years: 3 warm-up years and 4 years over which data were collected.

6.2.2 Weightings Used to Determine Improvements In Outcomes

The equity and utility measures recorded in Hepatica are detailed Section 3.4. The rest of this section identifies the key measures which were evaluated to give an overall picture of each scenario compared against the base scenario. Tables 6.1 and 6.4 outline the weightings that were used for calculating the overall equity and utility points derived for each scenario (as described in Section 3.4.3). These will be used to evaluate how the alternative scenarios affect equity and utility within the liver transplant system, compared to the base scenario. A number of different weightings were tested but all gave the same overall results and so the weightings below were implemented.

Equity

The two main equity measures which are analysed to obtain the overall impact of the scenarios, are:

(EM1) *Difference in Numbers to be Transplanted Across Groups* - this measure captures the extent to which a policy is allocating liver transplants fairly across different patient groups. Since there are only two outcomes from once a patient joins the waiting list (Death/Removal or Transplantation) only one outcome requires observation. This measure is assessed by summing up the differences between the expected and the observed number of patients to be transplanted from each group. The smaller the value obtained, the fairer the allocation of liver transplants has been. The patient groups considered are: centre, blood group, transplant number, primary liver disease group, weight, age, and gender. Once a value was calculated for an alternative scenario it was compared to the base scenario value. Then equity points were allocated based on whether the alternative scenario performed better, the same, or worse than the base scenario (as outlined further in Section 3.4.3).

(EM2) *Difference in Numbers to Experience Death/Graft Failure Across Groups* - this measure captures the differences in the proportion of patients from different groups experiencing the two post transplant outcomes of Death/Graft Failure and Re-Listing. Again, since there are only two outcomes from once a patient receives a transplant, only one outcome requires observation. This measure is assessed by summing up the differences between the expected and the observed number of patients to experience death/graft failure. The smaller the value obtained, the fairer the allocation policy has been in terms of

post-transplant survival chances. The patient groups considered are: centre, blood group, transplant number, primary liver disease group, weight, age, and gender. Once a value was calculated for an alternative scenario it was compared to the base scenario value. Then equity points were allocated based on whether the alternative scenario performed better, the same, or worse than the base scenario (as outlined further in Section 3.4.3).

Both EM1 and EM2 contribute to the overall assessment of equity (as presented in Sections 6.3-6.5). Table 6.1 shows that points obtained through the measure EM1 receive a higher weight than the points obtained through the measure EM2 when calculating the overall equity points; this is because the policy changes within the different scenarios and will directly impact on who is transplanted. The post transplant events will be a consequence of this.

Table 6.1 Equity Point Weightings.

	Equity Measure	Weighting
(EM1)	Waiting List Outcome	2
(EM2)	Post Transplant Outcome	1

Tables 6.2 and 6.3 give example calculations for the measures (EM1) and (EM2) for the base scenario.

Table 6.2 Calculation of Difference in Numbers to be Transplanted Across Groups (EM1) for the Base Scenario, B2.

Patient Group	Number to join the waiting list in simulation	Observed Number transplanted in the simulation (1)	Expected number transplanted in the simulation (2)	Absolute difference between observed and expected Abs {(1)-(2)}	Summed over group	Bias
All	28044	23055				
Centre A	1911	1512	1571	59	582	-
Centre B	4765	3759	3917	158		-
Centre C	2928	2504	2407	97		+
Centre D	2700	2213	2220	7		-
Centre E	7016	5946	5768	178		+
Centre F	5948	4823	4890	67		-
Centre G	2776	2298	2282	16		+
Blood Group O	12863	11878	10575	1303	2607	+
Blood Group A	11097	8367	9123	756		-
Blood Group B	2931	1870	2410	540		-
Blood Group AB	1153	940	948	8		-
First Transplant	24599	20342	20223	119	238	+
Successive Transplant	3445	2713	2832	119		-
All Other Diseases	8864	7231	7287	56	839	-
Other Cirrhotic	5028	4349	4134	215		+
Cancer	667	478	548	70		-
Other Diagnosed	1645	1457	1352	105		+
Super Urgent/Acute	5398	4537	4438	99		+
Hepatitis B	941	732	774	42		-
Alcoholic Disease	4827	3884	3968	84		-
Not Reported	674	387	554	167		-
Weight <=50kg	1571	1311	1292	19	166	+
Weight 51-65kg	8137	6753	6689	64		+
Weight 66-80kg	10303	8410	8470	60		-
Weight 81-99kg	6273	5138	5157	19		-
Weight 100kg and over	1760	1443	1447	4		-
Age <=25 years	1865	1626	1533	93	601	+
Age 25-35	2658	2299	2185	114		+
Age 36-45	5126	4308	4214	94		+
Age 46-55	8528	6985	7011	26		-
Age 56-65	8097	6455	6657	202		-
Age 66 and over	1770	1382	1455	73		-
Male	15358	12396	12626	230	460	-
Female	12686	10659	10429	230		+
EM1 (i.e., total)					5492	

Table 6.3 Calculation of Difference in Numbers to Experience Death/Graft Failure Across Groups (EM2) for the Base Scenario, B2.

Patient Group	Number to transplanted simulation	Observed Number to experience death of graft failure in the simulation	Expected number to experience death of graft failure in the simulation	Absolute difference between observed and expected	Summed over group	Bias
		(1)	(2)	Abs {(1)-(2)}		
All	23055	16984				
Centre A	1512	1100	1114	14	211	-
Centre B	3759	2814	2769	45		+
Centre C	2504	1800	1845	45		-
Centre D	2213	1691	1630	61		+
Centre E	5946	4377	4380	3		-
Centre F	4823	3514	3553	39		-
Centre G	2298	1688	1693	5		-
Blood Group O	11878	8712	8750	38	121	-
Blood Group A	8367	6219	6164	55		+
Blood Group B	1870	1383	1378	5		+
Blood Group AB	940	670	692	22		-
First Transplant	20342	14996	14985	11	21	+
Successive Transplant	2713	1988	1999	11		-
All Other Diseases	7231	5341	5327	14	83	+
Other Cirrhotic	4349	3188	3204	16		-
Cancer	478	359	352	7		+
Other Diagnosed	1457	1054	1073	19		-
Super Urgent/Acute	4537	3340	3342	2		-
Hepatitis B	732	543	539	4		+
Alcoholic Disease	3884	2857	2861	4		-
Not Reported	387	302	285	17		+
Weight <=50kg	1311	981	966	15	148	+
Weight 51-65kg	6753	4960	4975	15		-
Weight 66-80kg	8410	6241	6195	46		+
Weight 81-99kg	5138	3726	3785	59		-
Weight 100kg and over	1443	1076	1063	13		+
Age <=25 years	1626	1201	1198	3	75	+
Age 25-35	2299	1677	1694	17		-
Age 36-45	4308	3163	3174	11		-
Age 46-55	6985	5168	5146	22		+
Age 56-65	6455	4767	4755	12		+
Age 66 and over	1382	1008	1018	10		-
Male	12396	9129	9132	3	6	-
Female	10659	7855	7852	3		+
EM2 (i.e., total)					665	

Utility

As discussed in Section 2.3.2, it is important to gauge utility at all parts of the liver transplantation system, since we ideally want policies which create an effective system overall. The objective is essentially to make the best decisions in terms of providing the greatest good for the greatest number of patients.

Several measures were considered when evaluating utility (as discussed in Sections 3.4 and 3.4.2 and reported in Sections 6.3-6.5), however only the most important five measures contribute to the overall utility aspect considered in Hepatica. Table 6.4 summarises the weightings given to each of the aspects when calculating the overall utility points for a particular policy. All comparisons were made against the base scenario, as explained in Section 3.3.4.

Table 6.4 Utility Point Weightings.

Utility Measure		Weighting
UM1	Life Years in System per patient	1
UM2	Life Years Gained per Transplant	1
UM3	Number of Wasted Livers	1
UM4	% Death/Removals from waiting list	0.5
UM5	% Death/Graft Failure within 1 year of transplantation	0.5

The aspects considering life year in the system and life years gained ((UM1) and (UM2)) are important as they portray how effective the decision to transplant, or not to transplant particular patients, is. Another key measure is the number of livers wasted (UM3). This is used on the basis that if livers are wasted, then this implies that there are inefficiencies in the system. The percentage of patients to experience death or removal from the waiting list (UM4) and the percentage of patients to experience death or graft failure within one year of transplantation

(UM5) are also required as any utilitarian system should be looking to minimise the number of patients who experience these outcomes. These measures are given slightly less weight, since the main aim of liver transplantation is to improve the overall measures of patient survival.

6.3 Analysis of Outputs from Changing one Factor

This section reports on the results obtained from the ‘one factor’ changes as outlined in Sections 3.3.1-3.3.4. It uses the methodology outlined in Sections 3.4.3 and 6.2 to compare the equity and utility measures obtained with the results observed from the base scenario.

6.3.1 Demand Factors

The demand factors consider the effect of an increasing, or of a constant demand for liver transplantations, as detailed in Section 3.3.1. For the base scenario the average number of arrivals each year (excluding the number of patients re-listed) 613 (2,452 in total) The total number of extra arrivals over the 4 years simulated for the demand factors D2, D3, and D4, were 122, 193, and 146, respectively.

From Tables 6.5 and 6.6 it can be seen that when the demand for liver transplantation is increased and all other experimental factors are kept the same, the allocation system becomes less fair and the utility measures are also adversely affected.

Table 6.5 Utility Outputs from Demand Scenarios.

Demand Scenario		Life Years in System per Patient	Life Years Gained per Transplant	% Re-Listed within 1 yr	% Death/Graft Failure within 1 yr	% Death/Removal from WL	Weighted utility points
B2	Base case	23.9	26.4	5.20	14.40	17.80	
D2	Demand Increasing (122 extra patients over 4 years)	23.5	26.2	4.90	14.40	18.50	-0.5
D3	Demand Increasing (193 extra patients over 4 years)	23.4	26.3	5.20	14.50	18.90	-0.5
D4	Demand Increasing (146 extra patients over 4 years)	23.5	26.3	5.19	14.33	18.55	-0.5

Note: The Number of Wasted Livers is not presented in this table, since all the policies considered had 0 wasted livers, over the 4 years which were simulated.

Table 6.6 Equity Outputs from Demand Scenarios.

Demand Scenario		Waiting List Outcome	Post Transplant Outcome	Weighted equity points
B2	Base case	5492	665	
D2	Demand Increasing (122 extra patients over 4 years)	5996	627	-1
D3	Demand Increasing (193 extra patients over 4 years)	6185	814	-3
D4	Demand Increasing (146 extra patients over 4 years)	6687	778	-3

Over the 4 years simulated, significant differences were observed in the percentage of patients experiencing death or removal from the waiting list. As expected, this has arisen because the increase in demand has meant that a smaller proportion of patients are able to receive a transplant.

For the waiting list and post transplant equity outcomes, there was an overall negative bias in the patient groups transplanted, however there were no dramatic changes, and no particular losers or gainers amongst the patient groups. The effect of increasing the demand was simply to increase the biases present in the base scenario. In both cases, the patient groups who received priority – super urgent patients and those with blood group O – fared much better than other patients. As demand increases, this discrepancy was observed to become more pronounced.

Figure 6.1 shows the average number of patients on the waiting list over the 10 simulation runs, by simulated time, for the 4 demand factors. The size of the waiting list at the end of the 4 simulated years, are: 256, 276, 293, and 283, for the factors D1, D2, D3, and D4, respectively. Given that supply is insufficient (and constant) it is logical that the number of patients waiting for a transplant should increase as the demand for liver transplantation increases.

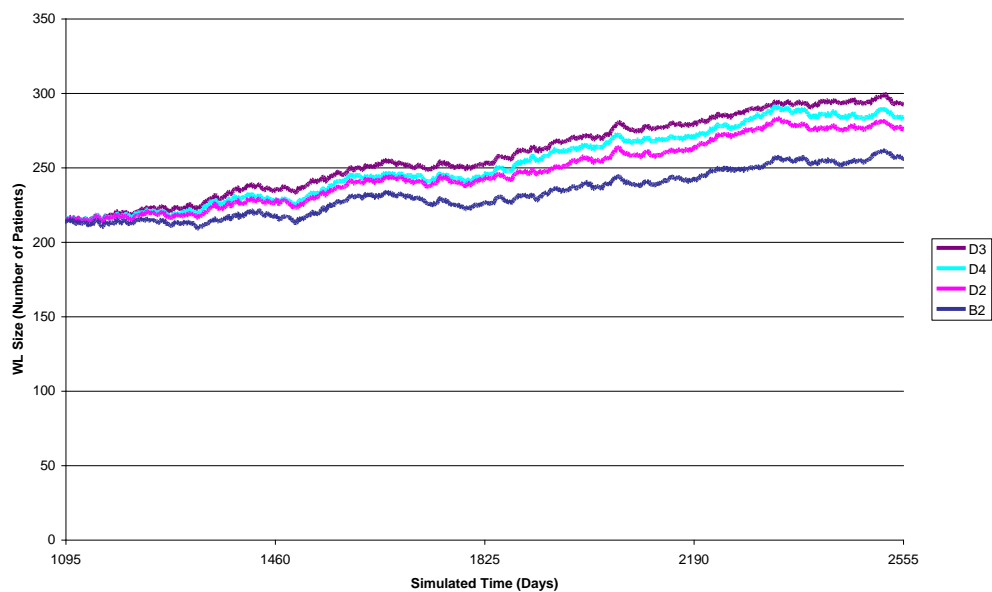


Figure 6.1 Size of Waiting List by time for the Demand Scenarios.

No significant changes were observed for the other measures, in particular, for the life year calculations only small decreases are observed. It is likely that the simulations performed have only started to see the effect of increasing the demand, and running the models for a longer period would result in more aspects becoming significant.

6.3.2 Supply Factors

The supply factors consider the affect of an increasing, a decreasing, or a constant supply of liver transplants, as detailed in Section 3.3.2. For the base scenarios the average number of donations per year was 561 (2,244 in total). The change in total number of liver donations over the 4 years simulated for the supply factors S2, S3, and S4, were a decrease of 398, an increase of 558, and an increase of 205, respectively.

From Tables 6.7 and 6.8 it can be seen that when the supply of liver transplants is decreased and all other experimental factors are kept the same, the allocation system becomes less fair and the utility measures are adversely affected. Conversely, the equity and utility of the system is significantly improved if the supply of livers is increased.

As the supply is increased, the number of patients receiving a transplant increases, hence there is a reduction in the proportion of patients experiencing death or removal from the waiting list and the number of life years in the system

increases (Table 6.7). The opposite is observed when the supply of livers decreases.

Table 6.7 Utility Outputs from Supply Scenarios.

Supply Scenario		Life Years in System per Patient	Life Years Gained per Transplant	% Re-Listed within 1 yr	% Death/Graft Failure within 1 yr	% Death/Removal from WL	Weighted utility points
B2	Base case	23.9	26.4	5.20	14.40	17.80	
S2	Declining donations (398 fewer over 4 years)	21.9	26.3	5.20	14.30	24.60	-1.5
S3	Increasing donations (558 more over 4 years)	24.6	26.0	5.10	14.30	14.00	1
S4	Increasing donations (205 more over 4 years)	23.8	26.2	5.00	14.20	17.20	0

Note: The Number of Wasted Livers is not presented in this table, since all the policies considered had 0 wasted livers, over the 4 years which were simulated.

Table 6.8 Equity Outputs from Supply Scenarios.

Supply Scenario		Waiting List Outcome	Post Transplant Outcome	Weighted equity points
B2	Base case	5492	665	
S2	Declining donations (398 fewer over 4 years)	7102	591	-1
S3	Increasing donations (558 more over 4 years)	4344	563	3
S4	Increasing donations (205 more over 4 years)	5112	642	2

When the supply is decreased the bias on the outcomes from the waiting list grew in magnitude and when the supply is increased the bias decreases (Table 6.8). The attribute which is affected the most is urgency of the transplant (Table 6.9). Super urgent patients receive priority over donated livers, so when the supply decreases routine patients will have less chance of receiving a transplant, but when the supply of donated livers increases their chances are greatly improved and the equity also improves.

Table 6.9 Outcome Differences for Transplant Urgency Status, from Supply Scenarios.

Urgency	EM1	EM2
B2	341	31
S2	731	6
S3	236	11
S4	22	53

Figure 6.2 shows the average number of patients on the waiting list over the 10 simulation runs, by simulated time, for the 4 supply factors. The size of the waiting list at the end of the 4 simulated years, are: 256, 439, 72, and 202, for the factors S1, S2, S3, and S4, respectively. The number of patients waiting for a transplant increases as the supply of liver transplants decreases.

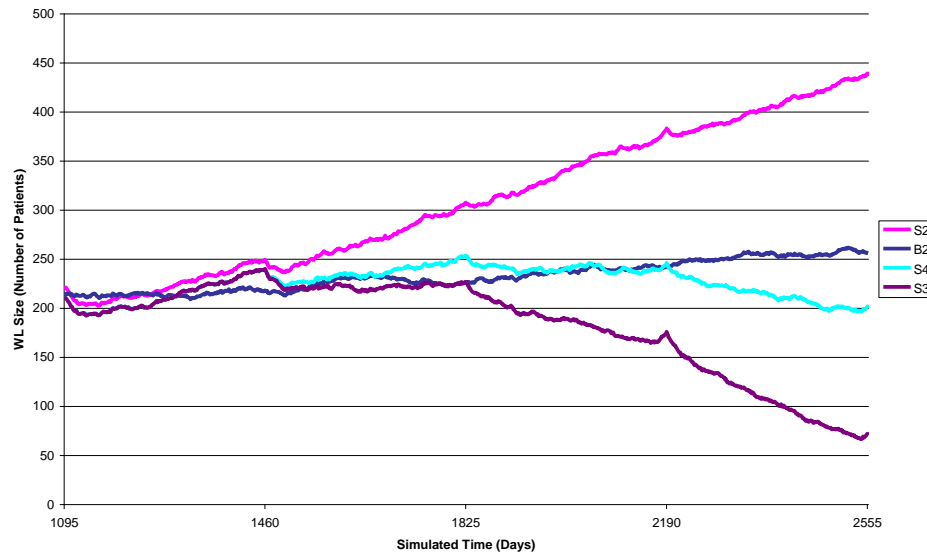


Figure 6.2 Size of Waiting List by time for the Supply Scenarios.

No significant changes were observed in the post transplant utility measures. This implies that the patient mix to be transplanted is similar across the four supply factors – at least in terms of the factors which impact on post-transplant survival.

6.3.3 Assessment Rule Factors

The assessment factors consider the effect of restricting the pre-transplant prognosis of patients who join the waiting list, as detailed in Section 3.3.3. The total number of patient and donor arrivals remains constant in all three scenarios. The only aspect altered is how long the patient is expected to live if they do not receive a transplant. Factor A2 reduces the times by 10% and factor A3 increases the times by 10%.

From Tables 6.10 and 6.11 it can be seen that as the pre-transplant prognosis worsens, the allocation system becomes less fair and the utility measures are

adversely affected. As the pre-transplant prognosis improves, the allocation system again becomes less fair, but the utility measures are improved.

As the pre-transplant prognosis worsens, the proportion of patients experiencing death or removal from the waiting list increases and the number of life years in the system decreases (Table 6.10), and vice versa when the pre-transplant prognoses of patients is better. When the pre-transplant prognosis of patients joining the waiting list is much lower, many more will die before a liver becomes available to them. A secondary result is that as more patients die, the size of the waiting list reduces. Ultimately this means that a number of livers are wasted as there are no suitable patients on the waiting list when the donated liver becomes available. There was no significant impact on post-transplant survival, implying that the characteristics of patients receiving a transplant is not affected that much.

Table 6.10 Utility Outputs from Assessment Scenarios.

Assessment Scenario		Life Years in System per Patient	Life Years Gained per Transplant	% Re-Listed within 1 yr	% Death/Graft Failure within 1 yr	% Death/Removal from WL	Weighted utility points
B2	Base case	23.9	26.4	5.20	14.40	17.80	
A2	10% poorer initial prognosis	22.5	26.5	5.10	14.30	20.40	-2.5
A3	10% better initial prognosis	24.9	26.0	5.30	14.30	14.40	1.5

Note: The Number of Wasted Livers is not presented in this table; B2 and A3 had 0 livers wasted, while A2 had 51 livers wasted per year, over the years simulated.

Table 6.11 Equity Outputs from Assessment Scenarios.

Assessment Scenario		Waiting List Outcome	Post Transplant Outcome	Weighted equity points
B2	Base case	5492	665	
A2	10% poorer initial prognosis	6501	691	-2
A3	10% better initial prognosis	6104	744	-3

Table 6.2 indicated that the base case scenario favours blood group O patients over patients with other blood types, as it gives them priority over any blood group O donations. There is currently a poorer supply of blood group A, B, and AB livers (Appendix B, Table B.2) and this is not sufficient to meet the demand of all patients with these blood groups. This shortfall can only be met by using organs donated by people with blood group O. The positive bias of transplants to blood group O patients is not noted under A2, which assumes the same allocation priorities as the base scenario. This is because there are fewer patients waiting (since patients die earlier) and therefore priority by blood group is not as important and patients with blood groups A, B, and AB do better. Similarly, patients requiring a routine transplant benefit under factor A2, since there are fewer patients on the waiting list, and so the fact that super urgent patients normally receive priority, becomes less important.

Figure 6.3 shows the average number of patients on the waiting list over the 10 simulation runs, by simulated time, for the 3 assessment factors. The size of the waiting list at the end of the 4 simulated years, are: 256, 14, and 680, for the factors A1, A2, and A3, respectively. The size of the waiting list is smaller for the scenarios where the prognosis of patients joining the waiting list is worse.

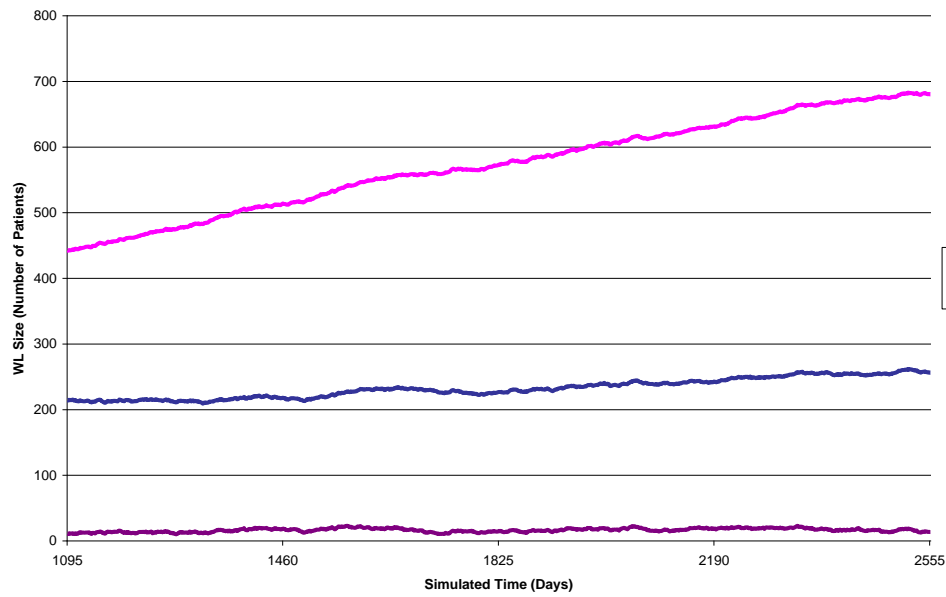


Figure 6.3 Size of Waiting List by time for the Assessment Scenarios.

6.3.4 Allocation Rule Factors

The allocation factors consider the affect of implementing various allocation rules, as detailed in Section 3.3.4. Changes were made to the allocation rules to influence seven main aspects:

- (1) Blood group matching and equity among blood groups;
- (2) Centre matching;
- (3) Liver transplant number
- (4) Patient age;
- (5) Time spent waiting for a transplant;
- (6) Patient weight compared to donor weight; and
- (7) Pre-/post-transplant prognosis and utility.

Tables 6.12 and 6.13 summarise the utility and equity outcomes recorded from the simulation. The findings from each aspect are summarised after the tables.

Table 6.12 Utility Outputs from Allocation Scenarios.

Allocation Priority To		Life Years in System per Patient	Life Years Gained per Transplant	% Re-Listed within 1 yr	% Death/Graft Failure within 1 yr	% Death/Removal from WL	Weighted utility points
B2	Base case	23.9	26.4	5.20	14.40	17.80	
L3	Compatible Blood Groups	23.4	25.8	5.40	15.20	17.70	-2.5
L4	Identical Blood Groups	23.9	26.4	5.00	14.00	17.60	0
L5	Local Patients	23.6	26.1	5.00	14.00	18.10	0
L6	National Patients	23.9	26.3	5.20	14.20	17.40	0
L7	First Transplants	23.5	26.2	4.80	13.50	18.80	0
L8	Successive Transplants	23.6	26.3	4.70	13.60	18.20	0.5
L9	Younger Patients	24.6	27.5	5.00	13.80	18.80	2
L10	Older Patients	22.2	24.7	5.00	14.00	18.60	-2.5
L11	Those waiting the shortest time	23.4	26.0	5.20	14.40	18.70	-2.5
L12	Those waiting the longest time	23.7	26.3	4.70	13.20	18.20	0.5
L13	Patients where the absolute difference between donor and patient weight is minimised	23.6	26.2	4.80	13.50	18.30	-1
L14	Patients with the soonest death or removal time (i.e., worst pre-transplant prognosis)	24.6	26.7	5.00	14.10	15.40	1.5
L15	Patients with the best post-transplant prognosis	29.4	33.3	3.60	10.50	18.10	2.5
L16	Patients with best prognosis compared to expected prognosis without a transplant	30.8	35.1	3.80	11.00	17.90	2.5
L17	An adaptive policy which attempts to make allocation decisions through keeping track of equity measures, for groups not fairly transplanted across, within the other allocation policies	23.7	26.1	5.20	14.70	17.60	0

Note: The Number of Wasted Livers is not presented in this table, since all the policies considered had 0 wasted livers, over the 4 years which were simulated.

Table 6.13 Equity Outputs from Allocation Scenarios.

Allocation Priority To		Waiting List Outcome	Post Transplant Outcome	Weighted equity points
B2	Base case	5492	665	
L3	Compatible Blood Groups	4972	665	2
L4	Identical Blood Groups	5071	747	1
L5	Local Patients	4690	797	1
L6	National Patients	5893	584	-1
L7	First Transplants	11232	642	-2
L8	Successive Transplants	9961	762	-3
L9	Younger Patients	5760	614	1
L10	Older Patients	13305	745	-3
L11	Those waiting the shortest time	5222	632	1
L12	Those waiting the longest time	10561	755	-3
L13	Patients where the absolute difference between donor and patient weight is minimised	9488	569	-1
L14	Patients with the soonest death or removal time (i.e., worst pre-transplant prognosis)	5324	1043	-1
L15	Patients with the best post-transplant prognosis	9393	645	-2
L16	Patients with best prognosis compared to expected prognosis without a transplant	9458	620	-1
L17	An adaptive policy which attempts to make allocation decisions through keeping track of equity measures, for groups not fairly transplanted across, within the other allocation policies	3376	697	2

(1) Blood Group Matching and Equity (B2, L3, L4, L17)

The number of life years in the system will be affected by changes in the number of patients experiencing death or removal from the waiting list, and also by changes in post transplant survival times. In factor L3 the number of life years gained was seen to significantly decrease and from Table 6.12 it would seem

that this happened because a significantly larger proportion of transplanted patients experienced post-transplant survival times shorter than one year.

Factor L3 imposes less stringent rules on blood group matching and hence a smaller percentage of transplants took place where there was an identical match between donor and patient blood groups when compared with the base scenario (as shown in Table 6.14). Hepatica uses identical blood group as a factor when generating post transplant survival times (Equation 4.6 Section 4.5.2) - because rejection is less likely when there is an identical match between blood groups. This would therefore explain the results observed for L3.

Table 6.14 Percentage of Transplants with Identical Donor and Patient Blood Groups.

	Percentage of Identical Matches	Identical blood matches	Total transplants
B2	97.7	2,253	2,306
L3	87.7	2,028	2,312
L4	99.7	2,299	2,306
L17	90.4	2,090	2,311

Policies which enforce identical donor and patient blood group matching more stringently will lead to an increase in the total gain in life years (e.g., policy L4). Table 6.14 shows the proportion of transplants which took place where there was an identical match between the blood types of the patient and donor. The extra life years gained under L4 is not actually significant, as the base scenario already had a very high proportion of transplants where the blood groups were identically matched.

L17 gives priority to patients from the blood group which has currently received the fewest number of transplants relative to size of this group (assuming that the blood groups of donor and patient are compatible). This policy significantly improves the equity of the system pre-transplant and does not affect the other outcomes greatly. The patients who miss out the greatest under this policy (compared to the base scenario) are those with blood group O. Overall this policy allocates more fairly than the base scenario, across the four blood groups.

(2) Centre Matching (B2, L5, L6)

The base scenario (B2) allocates livers to super urgent patients on a national basis and to routine patients initially within the retrieving centre. If no compatible match exists then they allocate nationally. L5 employs more stringent rules and allocates the donated livers locally within the retrieval centre first and then if no match is found, allocates nationally. L6 uses a more relaxed process and allocates all donated livers nationally.

Under the more stringent policy (L5) super urgent patients miss out on transplantation in favour of routine patients. This leads to greater equity in the system with regard to transplant centre and transplant urgency, but also leads to more super urgent patients dying or being removed from the waiting list. L5 also allocates more fairly across blood groups at the expense of blood group O patients.

L6 is similar to the base scenario in terms of its treatment of super urgent patients, however, biases increase in the treatment of routine patients, particularly between patients with different blood types.

(3) Transplant Number (B2, L7, L8)

L7 and L8 give priority to patients waiting for their first (L7) or successive liver transplant (L8). These policies both improve the equity in the system across blood groups when compared to the base scenario, albeit at the expense of patients with blood group O.

L7 leads to an increase in the number of routine patients receiving a transplant and exaggerates the bias in favour of patients waiting for their first transplant. This results in the policy being less fair pre-transplant. Under L7, more patients died from the waiting list but a significant improvement in post-transplant survival times was observed. The groups likely to suffer the most are those super urgent patients requiring a re-transplant, while the post-transplant survival times are likely to have benefited from the implicit bias towards younger and routine patients – who are expected to live longer post-transplant (Equation (4.6) Section 4.5.2).

By allocating to patients waiting for a successive transplant (L8), the bias changes direction towards patients waiting for a successive transplant, generally favouring older patients. This reduces the equity in the system, particularly across different patient age groups.

(4) Patient Age (B2, L9, L10)

L9 gives priority to younger patients, while L10 gives priority to older patients; with livers being allocated to the youngest (or eldest) patients on the waiting list.

In both scenarios, super urgent patients no longer have priority over routine patients, meaning that routine patients experience better outcomes when compared to the base scenario. This has a direct effect on the number of deaths of super urgent patients pre-transplant (Table 6.12). L9 results in a fairer system for patients waiting for their first transplant, but patients waiting for a successive transplant (generally super urgent patients) are put at a disadvantage.

Allocating to younger patients results in better overall post-transplant survival times, but the opposite is true when priority is given to older patients. This is consistent with the post-transplant survival model created, in which the age of the patient was found to be a significant factor.

Understandably, under L9 the bias against older patients is exaggerated, while under L10 the bias switches so that older patients receive more transplants.

(5) Time Spent Waiting for a Transplant (B2, L11, L12)

Allocating to patients either based on the shortest waiting times (L11) or the longest waiting times (L12) results in more routine patients being transplanted. This finding is intuitive for L12, for L11 it requires a bit more explanation. Firstly, super urgent patients will no longer have priority ahead of routine

patients that have recently been placed on the waiting list; indeed, there are far more routine patients than super urgent patients, so they will now receive a larger proportion of the livers available. Secondly, as more patients die or are removed from the waiting list, the list will reduce in size, giving routine patients more chance of receiving a donated liver. Super urgent patients, who are likely to die after a couple of days, are not so fortunate. Allocating to those patients who have been waiting the shortest time leads to a significant decrease in the number of life years gained and a decrease in the number of life years in the system. This is primarily because many more patients are experiencing death or removal from the waiting list.

(6) Patient Weight Compared to Donor Weight (B2, L13)

L13 allocates a donated liver by determining the patient whose weight is most closely matched with the donor's weight. The result of this is that the number of life years in the system significantly decreases as a consequence of a greater number of patients experiencing death or removal from the waiting list. The increase in death/removal from the waiting list is most likely to be due to the additional weight criteria having a negative impact on the number of super urgent patients receiving transplants. There are fewer super urgent patients and so it will be more likely that a routine patient will be a better match in terms of weight. As a result of weight matching, significantly better post transplant outcomes are experienced.

(7) Pre-/post-transplant prognosis and utility (B2, L14, L15, L16)

L14 allocates the donated livers by giving priority to patients with the worst pre-transplant prognosis. This significantly increases the number of life years in the system, and reduces the percentage of patients to experience death or removal from the waiting list. Table 6.15 shows how the number of patients on the waiting list significantly increases under this policy, as a result of fewer deaths/removals. Under this policy older patients gain as they are likely to have a worse pre-transplant prognosis (Equation (4.3) Section 4.4.2), this causes a great reduction in post transplant equity.

L15 and L16 both consider the likely survival chances of patients post transplant. L15 just looks to maximise this expected post transplant survival time, while L16 looks at maximising the difference between post-transplant and pre-transplant prognoses. Both policies result in significantly improving the life years in the system, the life years gained from transplant, and all post transplant outcome times.

However, both policies also result in overall biases increasing. The bias becomes greater against older patients and patients with smaller weights. These factors are all present in the formula which predicts post transplant outcome times (Equation (4.6) Section 4.5.2), and are all associated with shorter post-transplant survival times.

Routine patients receive more transplants under both L15 and L16. However, under L16 the bias towards routine patients is not as great as under L15. This is due to L16 seeking to maximise the life years gained from transplantation and therefore favouring super urgent patients who are expected to die very soon, but who also have a reasonable survival time post transplant, while L15 only considers who will have the best post transplant prognosis, which is shorter for super urgent patients (Equation (4.6) Section 4.5.2).

Table 6.15 Start and End Waiting List Size for all Allocation Factors.

	Allocation Priority to	Year 0 (1095 days)	Year 4 (2555 days)
B2	Base case	214	256
L3	Compatible Blood Groups	224	267
L4	Identical Blood Groups	204	243
L5	Local Patients	205	259
L6	National Patients	82	96
L7	First Transplants	90	104
L8	Successive Transplants	78	81
L9	Younger Patients	146	147
L10	Older Patients	101	101
L11	Those waiting the shortest time	136	139
L12	Those waiting the longest time	70	76
L13	Patients where the absolute difference between donor and patient weight is minimised	112	114
L14	Patients with the soonest death or removal time (i.e., worst pre-transplant prognosis)	441	598
L15	Patients with the best post-transplant prognosis	230	229
L16	Patients with best prognosis compared to expected prognosis without a transplant	194	238
L17	An adaptive policy which attempts to make allocation decisions through keeping track of equity measures, for groups not fairly transplanted across, within the other allocation policies	214	259

From Table 6.15 it can be seen that the waiting list size increases dramatically under L14. This is not unexpected as the policy attempts to allocate livers to patients who have the shortest time to death or removal, while the current policy in use does not consider this when allocating a liver to a routine patient. As a result of this, patients who have longer death or removal times will remain on the waiting list and fewer patients will die, so the waiting list size will increase. It is expected that eventually the number of patients on the waiting list would stabilise, as a steady stream of routine patients would die from the waiting list. Before the waiting list stabilised, there might be a critical point when the benefits of the policy are reduced. Two allocation policies result in much shorter waiting list sizes at the end of the four years, than all the other policies. These are allocation to patients requiring successive transplants (L8) and allocation to patients waiting the longest time (L12). Allocating to those waiting for their successive transplant or to patients who have been waiting the longest time, results in allocating few transplants to super urgent patients. This results in more deaths and removals from the waiting list, which in turn reduces the size of the waiting list.

Overall Equity and Utility - Allocation Rule Scenarios

From Figure 6.4 we can see that the only alternative allocation rule which, when compared with the current policy, improves both equity and utility within the liver transplantation system is L9 (giving priority to younger patients).

The allocation rules which improve the overall equity within the system, without adversely affecting the utility measures, are:

- L4 (priority to patients with identical blood group to the donor),
- L5 (priority to patients in the same centre as where the donor is retrieved, and
- L17 allocating maintaining compatible blood groups (i.e., to patients of the blood groups with proportionally the fewest transplants).

L15 and L16 increase utility most, but at the expense of equity within the system. Allowing allocation to any patient with a compatible blood group, (L3) does improve equity within the system, but to the detriment of the utility measures. Giving priority to older patients (L10) results in particularly bad outcomes with regard to both equity and utility. Allocating to patients who have most recently joined the waiting list (L11) improves equity, as in effect the liver transplants are being allocated to patients at random, but produces a far less effective system. Conversely, L12, which allocates to patients who have been on the waiting list the longest, is less equitable since patients with certain attributes will be more likely to benefit, as they can survive for longer before requiring a transplant.

The most promising policies (L4, L5 and L9) are considered further in Sections 6.4 and 6.5. L17 is not considered, as this policy is not practicable, however, it has been useful to demonstrate the potential impact of a policy which attempts to increase equity within the system.

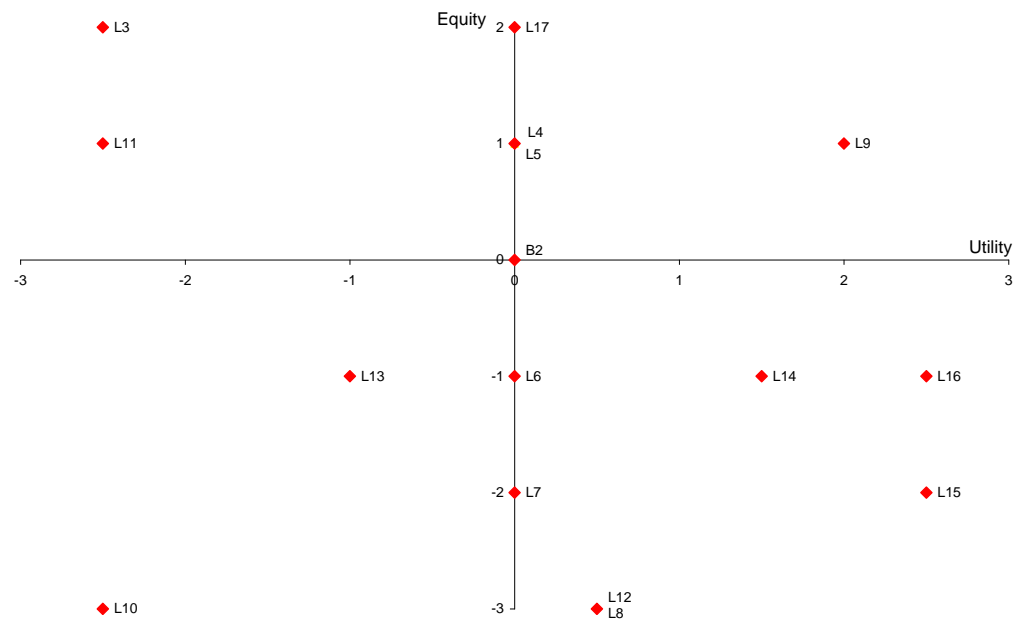


Figure 6.4 Equity Points Against Utility Points for the Allocation Scenarios.

6.3.5 Discussion of Findings

As the demand for liver transplantation increases, both equity and utility in the liver transplantation system are adversely affected. Utility is affected because the imbalance between supply and demand is increased, meaning that a greater proportion of patients experience negative outcomes. Equity is also affected as the system in place gives priority to super urgent patients and patients with blood type O. As demand increases, patients with other characteristics become even less likely to receive a transplant. Essentially, the biases present in the base scenario are exaggerated as the imbalance between supply and demand increases.

Similarly, a declining supply of livers results in a much greater bias towards super urgent patients being transplanted. As supply is increased many more routine patients were transplanted, and vice versa. The same pattern is observed

between patients with blood type O and with patients from other blood groups. It was found that as the supply of donated livers increases, it will still take approximately two years before the size of the waiting list begins to fall.

The overall effect of restricting the assessment criteria, so that only patients with worse prognosis are allowed onto the waiting list, is to decrease the number of life years in the system. In these scenarios, the pre-transplant prognoses of patients are worse, meaning that they will die earlier, and are less likely to receive a transplant in the meantime. As a secondary consequence, a number of livers would be wasted as there could be no suitable patients on the waiting list. As the assessment criteria is restricted to only allowing patients with better prognosis onto the waiting list, the number of life years in the system increases. Both policies are biased in terms of which patient groups benefit from transplantation.

One desirable feature of the base scenario is that by giving priority to blood group O patients (when a blood group O liver is donated) it does encourage identical blood group matching. However, due to the mismatch between donor blood groups and patient blood groups (Table B.2 Appendix B), enforcing only identical blood group matched transplants (L4), does significantly disadvantage blood groups AB, B, and A.

A more stringent centre matching policy leads to super urgent patients missing out on a transplant but increases equity amongst patient blood groups. This is

because when a liver is donated, it will be allocated first to a compatible patient within the centre, irrespective of whether a super urgent patient is waiting elsewhere. Local populations of donors and patients will have similar ethnicity and so similar blood groups, and so it is likely that this helps to improve the equity amongst the different blood groups.

Implementing policies which give priority to patients waiting for either their first transplant or a successive transplant, affected the proportions of patients transplanted by urgency. For the policy which gave priority to patients waiting for their first transplant, fewer super urgent patients were transplanted. The pre-transplant survival times are then dominated by these super urgent patients, who die sooner, hence the proportion to death/removal from the waiting list increases. The post-transplant survival times are dominated by the routine patients and so the number of deaths/graft failures (within 1 year of transplantation) and re-lists (within 1 year of transplantation) were seen to decrease. Similar effects were noted from giving younger or older patients priority for transplantation.

Allocating livers according to the time (shorter or longer) a patient has spent on the waiting list results in better outcomes for the routine patients and worse outcomes for super urgent patients, with more deaths and removals from the waiting list. Allocating to those who have spent a shorter time on the waiting list leads to fewer life years in the system and life years gained from transplant, and better post transplant equity. Allocating transplants to minimise the weight

difference between the patient and donor also disadvantages super urgent patients.

Allocating transplants to the patient with the worst pre-transplant prognosis at the time when a liver is donated has the effect of reducing the number of patients who die from the waiting list and increasing the overall life years in the system, as well as reducing some of the bias present in the base scenario. The policies which use post-transplant prognosis improve all utility measures except the proportion of patients who die/are removed from the waiting list, which worsens slightly. These policies also lead to the system becoming more biased towards younger, routine, male patients who will remain alive for longer post transplant, and patients who are heavier.

6.4 Analysis of Outputs from New Allocation Rules

As identified in Sections 6.3.4 and 6.3.5, the most promising allocation policies identified are: L4 (priority to patients with an identical blood group to the donor's), L5 (priority to patients from the same centre as the donor), and L9 (priority to younger patients). Since these allocation rules can be combined (e.g., (L4) and (L9) combined would give priority to younger patients with identical blood groups) several new rules were devised and these were used in further simulation runs. The factors that received priority were always the ones which had performed better initially, as reported in Section 6.3.4. The new rules considered were: L4L5, L4L9, L5L9, and L4L5L9.

6.4.1 New Allocation Scenarios

Tables 6.16, 6.17 and Figure 6.5 show that when these allocation factors are combined, the resulting policy negatively impacts on both the utility and equity within the liver transplantation system. In particular, all of the new allocation policies resulted in worse outcomes for super urgent patients. This will have arisen because no priority is given to super urgent patients and because the additional criteria imposed make it more likely for a routine patient to be allocated a donated liver over a super urgent patient. As there are a greater number of routine patients on the waiting list, it is more likely that they will satisfy the criteria ahead of any super urgent patients on the list.

Table 6.16 Utility Outputs from the New Allocation Scenarios.

New Allocation Scenarios (Priority To)		Life Years in System per Patient	Life Years Gained per Transplant	% Re-Listed within 1 yr	% Death/Graft Failure within 1 yr	% Death/Removal from WL	Weighted utility points
B2	Base case	23.9	26.4	5.20	14.40	17.80	
L4L5	Identical blood groups and local centre	22.8	25.3	4.97	13.74	18.22	-2
L4L9	Identical blood groups and youngest	23.3	26.0	5.01	14.01	18.80	-1.5
L5L9	Local centre and youngest	23.0	25.7	4.97	13.77	18.65	-2
L4L5L9	Identical blood group, local centre and youngest	23.3	25.9	4.84	13.65	18.65	-1.5

Note: The Number of Wasted Livers is not presented in this table, since all the policies considered had 0 wasted livers, over the 4 years which were simulated.

Table 6.17 Equity Outputs from the New Allocation Scenarios.

New Allocation Scenarios		Waiting List Outcome	Post Transplant Outcome	Weighted equity points
B2	Base case	5492	665	
L4L5	Identical blood groups and local centre	5789	694	-2
L4L9	Identical blood groups and youngest	7190	672	-3
L5L9	Local centre and youngest	6539	603	-1
L4L5L9	Identical blood group, local centre and youngest	7504	864	-3

All factors which give younger patients priority for receiving a transplant (i.e., L4L9, L5L9, and L4L5L9) increase the bias towards younger patients being transplanted.

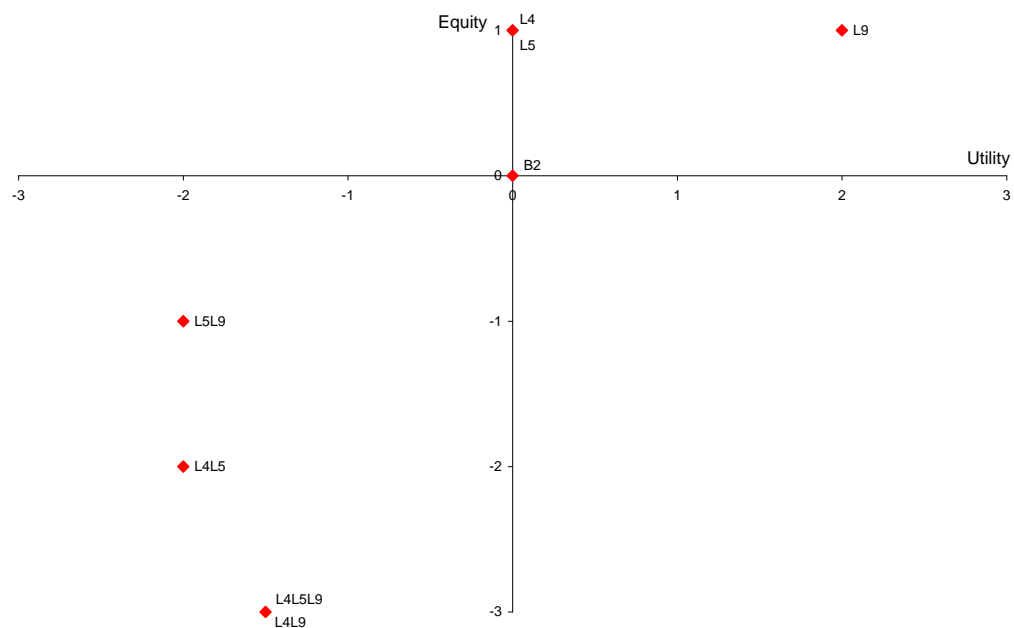


Figure 6.5 Equity Points Against Utility Points for the New Allocation Scenarios.

6.4.2 Discussion of Findings

All combinations were found to improve post transplant survival, albeit at the expense of more patients dying from the waiting list. Overall, therefore, the utility of the system is lower than the base scenario. Equity within the system is worse for all scenarios and indicates that the allocation rules favour certain groups of patients over others. This suggests that within the liver transplantation system there is no real advantage to developing complicated allocation policies – simple policies are likely to be at least as effective.

6.5 Analysis of Outputs from Full Factorial Experiments

The next stage of the analysis is to look at how these individual factors interact with each other. These full factorial experiments were constructed using the assessment rules, demand and supply factors which portrayed the situations that are considered to be the most realistic. The allocation rule factors which were chosen were identified as the most promising rules, from the analysis presented in Sections 6.3.4 and 6.3.5, at improving equity and utility within the liver transplantation system.

The factors considered for the full factorial experiment, are:

- Demand
 - A constant demand (D1); and
 - An increasing demand (D4).
- Supply

- A constant supply (S1); and
- A declining supply (S2).
- Assessment
 - Current assessment criteria (A1).
- Allocation
 - Base priority rules (B2);
 - Priority to patients with an identical blood group to the donor's (L4);
 - Priority to patients from the same centre as the donor (L5); and
 - Priority to younger patients (L9).

Since Section 6.4 shows that combining the allocation factors adversely affects the overall outcome measures. These combinations were not considered within the full factorial experiment.

6.5.1 Full Factorial Experiments

Table 6.18 outlines the scenarios considered in the full factorial experiments.

Table 6.18 Utility Outputs of Full Factorial Scenarios.

Key	Demand	Supply	Allocation
B2	Constant over time	Constant over time	Base case rules
L4	Constant over time	Constant over time	Priority to Identical Blood Groups
L5	Constant over time	Constant over time	Priority to Same Centre
L9	Constant over time	Constant over time	Priority to Younger Patients
D4	Demand Increasing (146 extra patients over 4 years)	Constant over time	Base case rules
L4D4	Demand Increasing (146 extra patients over 4 years)	Constant over time	Priority to Identical Blood Groups
L5D4	Demand Increasing (146 extra patients over 4 years)	Constant over time	Priority to Same Centre
L9D4	Demand Increasing (146 extra patients over 4 years)	Constant over time	Priority to Younger Patients
S2	Constant over time	Declining donations (398 fewer over 4 years)	Base case rules
L4S2	Constant over time	Declining donations (398 fewer over 4 years)	Priority to Identical Blood Groups
L5S2	Constant over time	Declining donations (398 fewer over 4 years)	Priority to Same Centre
L9S2	Constant over time	Declining donations (398 fewer over 4 years)	Priority to Younger Patients
D4S2	Demand Increasing (146 extra patients over 4 years)	Declining donations (398 fewer over 4 years)	Base case rules
L4D4S2	Demand Increasing (146 extra patients over 4 years)	Declining donations (398 fewer over 4 years)	Priority to Identical Blood Groups
L5D4S2	Demand Increasing (146 extra patients over 4 years)	Declining donations (398 fewer over 4 years)	Priority to Same Centre
L9D4S2	Demand Increasing (146 extra patients over 4 years)	Declining donations (398 fewer over 4 years)	Priority to Younger Patients

From Tables 6.19 and 6.20 (and as discussed in detail in Sections 6.3.4 and 6.3.5), the three allocation factors L4, L5, and L9 improve the overall equity, without adversely affecting the overall utility.

Table 6.19 Utility Outputs of Full Factorial Scenarios, which assume a Constant Demand and Supply.

Full Factorial Scenarios	Life Years in System per Patient	Life Years Gained per Transplant	% Re-Listed within 1 yr	% Death/Graft Failure within 1 yr	% Death/Removal from WL
B2	23.9	26.4	5.20	14.40	17.80
L4	23.9	26.4	5.00	14.00	17.60
L5	23.6	26.1	5.00	14.00	18.10
L9	24.6	27.5	5.00	13.80	18.80

Table 6.20 Equity Outputs of Full Factorial Scenarios, which assume a Constant Demand and Supply.

Full Factorial Scenarios	Waiting List Outcome	Post Transplant Outcome
B2	5492	665
L4	5071	747
L5	4690	797
L9	5760	614

Table 6.21 Utility Outputs of Full Factorial Scenarios, which assume an Increasing Demand and a Constant Supply.

Full Factorial Scenarios	Life Years in System per Patient	Life Years Gained per Transplant	% Re-Listed within 1 yr	% Death/Graft Failure within 1 yr	% Death/Removal from WL
D4	23.5	26.3	5.19	14.33	18.55
L4D4	23.6	26.4	5.04	14.19	18.62
L5D4	22.5	25.1	4.97	13.92	18.94
L9D4	24.2	27.6	5.09	13.81	20.09

Table 6.22 Equity Outputs of Full Factorial Scenarios, which assume an Increasing Demand and a Constant Supply.

Full Factorial Scenarios	Waiting List Outcome	Post Transplant Outcome
D4	6687	778
L4D4	5633	679
L5D4	4712	739
L9D4	8975	489

Tables 6.21 and 6.22 give the results from all the scenarios which consider an increasing demand. When there is a greater demand, it was found that:

- Prioritising identically matched transplants no longer improves any aspects of utility, however, does improve on post transplant equity;
- Allocating to patients from the same centre, results in a negative impact on the number of life years gained per patient and per transplant, but again improves on post-transplant equity; and
- Allocating to younger patients results in a negative impact on the equity achieved from the waiting list.

Table 6.23 Utility Outputs of Full Factorial Scenarios, which assume a Constant Demand and a Declining Supply.

Full Factorial Scenarios	Life Years in System per Patient	Life Years Gained per Transplant	% Re-Listed within 1 yr	% Death/Graft Failure within 1 yr	% Death\Removal from WL
S2	21.9	26.3	5.20	14.30	24.60
L4S2	21.9	26.4	5.02	14.19	24.55
L5S2	20.8	24.9	5.04	13.77	24.27
L9S2	22.1	28.6	4.90	13.68	29.70

Table 6.24 Equity Outputs of Full Factorial Scenarios, which assume a Constant Demand and a Declining Supply.

Full Factorial Scenarios	Waiting List Outcome	Post Transplant Outcome
S2	7102	591
L4S2	5446	601
L5S2	5421	854
L9S2	8372	490

Tables 6.23 and 6.24 give the results from all the scenarios which consider an declining supply. When there is a smaller supply, it was found that:

- Prioritising identically matched transplants no longer improves any aspects of utility, however, does continue to improve waiting list outcome equity;
- Allocating to patients from the same centre, results in a negative impact on the number of life years gained per patient and per transplant; and
- Allocating to younger patients results in a negative impact on the equity achieved from the waiting list.

Table 6.25 Utility Outputs of Full Factorial Scenario s, which assume an Increasing Demand and a Declining Supply.

Full Factorial Scenarios	Life Years in System per Patient	Life Years Gained per Transplant	% Re-Listed within 1 yr	% Death/Graft Failure within 1 yr	% Death/Removal from WL
D4S2	21.5	26.3	5.25	14.50	25.69
L4D4S2	21.7	26.5	5.14	14.17	25.38
L5D4S2	20.3	24.7	5.13	13.66	25.33
L9D4S2	21.9	28.9	4.98	13.70	30.93

Table 6.26 Equity Outputs of Full Factorial Scenarios, which assume an Increasing Demand and a Declining Supply.

Full Factorial Scenarios	Waiting List Outcome	Post Transplant Outcome
D4S2	6273	516
L4D4S2	5633	632
L5D4S2	5256	836
L9D4S2	8975	695

Tables 6.25 and 6.26 give the results from all the scenarios which consider both an increasing demand and a decreasing supply. Under this situation, it was found that:

- Prioritising identically matched transplants no longer improves any aspects of utility;
- Allocating to patients from the same centre, results in a negative impact on the number of life years gained per patient and per transplant; and
- Allocating to younger patients results in a negative impact on the equity achieved from the waiting list.

Overall, under the various demand and supply scenarios, it was found that allocating to identically matched patients did not improve on utility as before, allocating to younger patients maintained better utility and allocating to patients at the same centre negatively impacted on the overall utility. Allocating to younger patients had a negative impact on equity, while equity improved or remained the same when allocating to patients at the same centre or which identical blood groups to the donors.

6.5.2 Discussion of Findings

The results from the full factorial experiments identified that the allocation rule that performs the best in terms of utility under all the supply and demand scenarios is allocating to younger patients (L9). L9 also performs the worst in terms of equity, since it greatly exaggerates the biases against older patients.

Under each of the demand and supply scenarios, the waiting list size reaches an equilibrium after 2 years.

Increasing supply does not result in a drastic improvements to equity due to inherent biases within the allocation policies.

Due to the dynamics involved within equity and utility outcomes, if supply goes down or demand increases then it becomes increasingly hard to design a policy which is both equitable and maximises utility, while acknowledging the priority that should be allocated to patients requiring super urgent transplants.

6.6 Summary

This chapter summarised the results obtained from experimentation carried out using Hepatica. The results from changes in the demand, supply, assessment rules, and allocation rules are reported. New allocation rules were created based on the initial ‘one factor’ changes which improved both utility and equity outcomes. The most likely demand, supply and assessment factors and allocation factors which improve the system outcomes were then used in a full

factorial experiment. Under each of the demand and supply scenarios, the waiting list size reached equilibrium after roughly two years.

Overall the utility of donated livers is easier to improve than the overall equity in the system, under any policy which attempts to prioritise patients for liver transplantation. The biggest gains for both equity and utility resulted from the scenarios in which the patients expected to survive longer receive priority for transplantation (L4: identically matched blood groups, L5: routine patients, gained over super urgent, L9: younger and first transplant patients gained). However, when changing the future supply of liver transplants and the future demand for liver transplantation, this limits the overall impact of the allocation scenarios.

Several effects were found, in particular, when the overall supply increased at a greater rate than demand, the routine patients benefit, but when the overall supply decreases, routine patients lose out even more since there are fewer transplants and the super urgent patients receive priority for these. Similarly, when the overall supply decreased at a greater rate than demand, patients with blood groups A, B and AB missed out, as blood group O patients receive priority over any livers available. When supply increases, patients with different blood types have a more even chance of receiving a transplant.

All combinations (of policies L4, L5 and L9) improve post transplant survival. However, this is at the expense of more patients dying from the waiting list,

therefore the overall affect on utility is negative when compared to the base scenario. Equity is worse for all these scenarios and this implies that the allocation rules favour certain groups of patients over others. This suggests that within the liver transplantation system it is best to keep liver transplant allocation rules simple.

The key points to emerge from the analysis are that it is important to keep rules simple in order not to introduce too much bias into the system. Due to the inherent need to prioritise by transplant urgency there is a limit as to the improvements which can be gained within the equity and utility measures.

Chapter 7

Conclusions

7.1 Introduction

This chapter summarises the work performed in this thesis. It outlines the methodology that was used to meet the objectives of the work, the conclusions reached for the research questions posed, the limitations of the work and identifies areas of further work. This chapter also summarises some general conclusions and reports what was learnt from the work.

7.2 Problem Situation and Literature Review

When a person falls ill with end stage liver disease the only effective treatment that is currently available is a liver transplant. Although alternative treatments are being developed, in most cases the livers are provided from cadaveric donors. The prevalence of liver-related diseases is on the increase and the amount of unmet demand is unknown. Chapter 1 discusses this shortage in supply compared to the number of patients who require the operation, and explains that this shortfall is expected to worsen in the near future.

There are many conflicting opinions about which patients are suitable for transplant and how donated livers should be allocated. This, and the current shortage of donors, means that it is important to understand how various policies affect the outcomes experienced by the patients with end stage liver disease. There are two key stages within the liver transplantation process at which changes in policy can affect who joins the waiting list (assessment stage) and which patients receive a transplants (allocation stage). The policies chosen will determine the outcomes that individual patients will experience, as well as the overall effectiveness and fairness of the system.

There is a large amount of literature on Transplant Matching Models, but relatively few published studies which consider the UK Liver Transplant System. This literature was discussed in Chapter 2 and several limitations of the previous models were identified. While there have been several detailed transplant matching studies in the USA, the set up of the liver transplantation system in the USA is inherently different to the liver transplantation system in the UK.

Most previous models make little attempt to consider future changes in demand and supply for liver transplantation. However, due to the likely increasing gap between future need and future donations, it is necessary to understand whether different policies would be more appropriate in different situations.

Many of the previous models adopt a utilitarian approach when determining which patient should receive a liver transplant from all those on the waiting list. By focusing solely on the benefit gained from a potential transplant, it is likely that certain groups of patients will be disadvantaged if their survival chances post-transplant are relatively low. This is particularly likely to be true of older patients and patients with diseases that are liable to recur.

The sole UK model (Eldabi *et al.* 2001) just considers the cost-effectiveness of alternative allocation policies, and only concentrates on two disease groups. As such, it is limited on its ability to assess the equity of the system under these different policies. Significantly, it also does not include super urgent patients in the model. As these patients receive priority for any liver that is donated, their inclusion is crucial to be able to accurately model the liver transplant system.

The literature review identified some gaps in previous research which the work within this thesis aims to fill. These are the need to:

- Incorporate supply and demand;
- Monitor all patient groups;
- Balance the outcome measures equity and utility; and
- Consider assessment criteria restrictions, in the UK liver transplant system.

These are the main contributions this thesis makes to transplant matching studies.

From the literature three main aspects were identified which require consideration when building a model to represent the liver transplantation system; these are:

- (1) The identification of suitable measures for comparison between policies;
- (2) The identification of techniques by which to estimate the time a patient remains in a particular state; and
- (3) The identification of a methodology by which to model patient progression through the system.

7.3 Research Objectives and Methodology Implemented

This section reports on the methodology which has been implemented and to what extent the analysis performed has met the research objectives stated in Chapter 2.

7.3.1 Suitable Measures to Enable Comparison Between Policies

The identification of suitable measures to enable comparison between policies.

The overall aim of the analysis was to identify scenarios where all patients had an equal chance of receiving a liver transplant at the same time as maximising the effectiveness provided by the scarce liver transplants. Thus, equity and utility measures were used to look at the fairness and effectiveness of various scenarios. The equity and utility measures considered in the Discrete Event Simulation (DES) model were those from once a patient joins the waiting list.

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The utility measures considered are:

- Life years in the system per patient;
- Life years gained per transplant;
- Percentage of patients re-listed within 1 year of receiving a transplant;
- Percentage of patients to experience death or graft failure within 1 year of receiving a transplant; and
- Percentage of patients to experience death or removal from the waiting list, and the number of livers wasted.

The level of equity within the system was also considered by looking at the outcomes that different patients experienced following their arrival onto the waiting list, and post-transplant. Ideally, the chances of experiencing these outcomes would be independent of:

- The transplant centre;
- The patient's blood group;
- The number of previous transplants the patient had received;
- The disease type that the patients was suffering from; and
- The patient's age, weight and gender.

The differences by transplant urgency status were also analysed, but did not contribute to the overall equity measures.

The individual utility and equity measures were then weighted and combined to give the overall equity and utility of the system, and plots were created to compare changes in these measures across different allocation policies.

7.3.2 Estimating Events and Survival

The identification of a technique by which to estimate the time a patient will stay in a particular state (events and survival).

A logistic regression model was developed to take into account patient attributes for capturing the decision made of whether patients should join the waiting list, or not. It was decided not to use this model within the final DES model due to concerns about the validity of the results it produced. In particular, the model developed only captures the assessment decisions within one particular liver transplant centre. The characteristics of patients treated by this centre were shown to be significantly different to patients from other transplant centres, and the assessment rules are also thought to be interpreted differently by different centres. For these reasons it was decided not to rely on the logistic model created, and instead patients would be modelled from their arrival onto the waiting list. Changes to the assessment criteria were instead simulated by changing the prognosis of patients joining the waiting list.

The time until patients experienced death or removal from the waiting list was modelled using parametric competing risk models. The time until patients experienced death, graft-failure or re-listing following their transplant was modelled using parametric survival models. These models were then incorporated within the DES model, using Monte Carlo sampling techniques to determine how long a particular patient spent in a particular state. The main advantage of the survival techniques used is that the models can take into

account censored information resulting from the restrictions on the study period used.

The competing risks model enabled the modelling of times to the two main events from once a patient joins the waiting list:

- (1) Death or Removal; and
- (2) Transplantation.

The chosen method resolves the basic limitation of Survival Analysis that all censored event times should be independent of a cause, i.e. uninformative. The distributions developed for the Death/Removal outcome were then used within Hepatica.

All of the models were created using patient, donor and transplant risk factors that were easily attainable for all cases, taking into account the outcomes of all adult patients who joined the liver transplant waiting list within the study period. A detailed analysis of disease progression was not required due to the short times patients are expected to spend on the waiting list. As a result, only the main clinical measures were used in the analysis.

7.3.3 Patient Progression

The identification of a methodology by which to model patient progression through the system.

A Discrete Event Simulation was built to model the UK Liver Transplantation system, with a view to assessing whether alternative assessment rules and alternative transplant allocation policies improve upon the current rules and policies in place. DES was chosen to model patient progression over other methods. The main advantages that this technique offers is that it can allow for the modelling of patient- and donor-level interactions, it can capture the variation within the system, and allows for previous patient, donor and transplant characteristics to all aid in determining the transition times in future states (i.e., it can retain patient disease history).

The DES model was designed to output the equity and utility measures required to compare alternative scenarios. Statistical sub-models were developed and sampled from to estimate the times patients spent in particular states within the DES model.

Different scenarios were run to assess the impact on the equity and utility measures of changes to future demand and supply, and to the assessment and allocation policies in place. Expectations of future demand and supply were identified from published work, the new assessment criteria restricted the type of patients eligible for transplantation, and the allocation policies were identified as those which could feasibly be implemented and also those which were designed to improve either equity or utility within the system.

7.4 Research Questions and Key Findings

This section considers the research questions posed at the end of Chapter 2 and summarises the key findings of the work performed.

7.4.1 Suitable Measures to Enable Comparison Between Policies

‘Can we get a better understanding of whether alternative allocation policies can improve both equity and utility, simultaneously?’

The equity analysis of the base scenario presented in Chapter 6, confirmed that the base scenario is not equitable, with differences in outcomes observed across patient characteristics (blood group, disease group, age, centre) which determine how a donated liver is currently allocated to a particular patient on the waiting list.

Hepatica was used to model various scenarios and analyse how alternative allocation policies impacted on the equity and utility of the system, given the current level of supply and demand and the assessment criteria in place. Three allocation policies were found to improve on either the equity or utility of the system, without adversely affecting the other. These were policies which aim to:

- (1) Allocate to patients with an identical blood group to the donor;
- (2) Allocate to younger patients; and
- (3) Allocate to patients who were at the same centre that the liver was retrieved.

An additional policy was designed to address the main inequality in the system – patient blood group. This policy gave priority to the blood groups which proportionally had received the fewest number of transplants so far, ensuring that all transplants took place between patients and donors with compatible blood groups. This policy succeeded at improving the equity within the system, but at the expense of adversely affecting the utility of the system.

A further policy was designed to try and obtain the maximum utility of the system. This policy allocated each liver to the patient who would receive the largest benefit from that transplant – in terms of life expectancy. This policy succeeded at improving the utility of the system, but at the expense of adversely affecting the equity within the system.

‘Does the complexity of the allocation rules affect the equity and utility outcomes?’

The allocation rules which improved both equity and utility were combined to try and create an even better policy. The resulting allocation rules adversely affected both equity and utility, as a result of introducing more biases within the system. This suggests that for the examples considered it was a mistake to combine the allocation rules (making them more complicated), and that it may be better to keep allocation rules quite simple.

‘Do the policies which improve equity and/or utility, continue to do so as demand and supply change?’

The base scenario allocation rules and the allocation rules which improved both the equity and utility were then used in scenarios in which demand and supply changed over time. The analysis performed indicated that it is hard to balance both equity and utility over the long term. Over time the patient mix will change, as will the number of donations and patients requiring transplants. Any allocation policy which needs to prioritise patients, will inherently impose biases within the system, and due to changes in the patient mix, the magnitude and direction of the biases will be affected. The life years gained will implicitly be affected by the direction and extent of the biases, as many patient characteristics determine the eventual timings and outcomes the patients experience. Thus, the policy which provides the most benefits is dependent both on supply, demand, and the mix of patients requiring a liver transplant.

7.4.2 Estimating Events and Survival

‘Can we find a parametric distribution using statistical techniques that can be sampled from within a DES?’

It was possible to develop statistical models to capture the outcomes: from assessment, from the waiting list, and from transplantation. To capture the times to events from the waiting list and post transplantation, it was necessary to use very specialised techniques, to incorporate censored data and multiple risks. As

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a result, distributions which captured the outcomes and times were complex, but it was then possible to use these distributions within the DES model.

The models developed help to show which patient characteristics affect their progression through the system, and the likely outcomes that they will experience.

Patient age was found to be significant at all stages in the transplant system. Older patients were less likely to initially be placed on to the waiting list. They were also modelled to experience death or removal from the waiting and death/graft failure/re-listing outcomes sooner than younger patients.

Transplant urgency is another factor which unsurprisingly has an affect on the outcomes that a patient experience. As super urgent patients have very low pre-transplant life expectancy they were found to be much more likely to be listed onto the waiting list, and are given priority over livers that are donated. As well as having a very low pre-transplant life expectancy, they were also found to have to experience death/graft failure/re-listing following a transplant sooner than routine patients.

The Model for End stage Liver Disease (MELD) score is significant in determining who is listed for transplant, and the patients recovery post transplant. However, MELD does not appear significant in the waiting list outcome model. This may be unexpected as the MELD score is used in the

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USA to determine how ill a patient is when on the waiting list. The main limitation of the MELD score in this study is that we could only capture it at the stage at which patients were either assessed at Birmingham Liver Unit or at the time of transplant. MELD score is a clinical measure which will change over time and so for any definite conclusions we would need to monitor it at more observation points (e.g., daily or weekly intervals), and capture how the MELD score changes over time.

Patients with liver disease due to unknown causes, Cryptogenic cirrhosis, alcoholic cirrhosis, and the Hepatitis C Virus, were less likely to be placed on the waiting list initially. On the whole, alcoholic liver disease patients were found to experience longer survival times post transplant. Liver diseases due to cancer, Hepatitis B, or a missing diagnosis were seen to experience shorter times to death or removal once on the waiting list, but were not significantly different within the post transplant survival times. Patients suffering from other cirrhotic diseases (primary biliary cirrhosis, autoimmune cirrhosis or secondary biliary cirrhosis) experienced significantly longer survival times both while on the waiting list and post transplant, while patients in the category “other diagnosed liver disease” were seen to do well on the waiting list and have significantly shorter times to post transplant outcomes.

Other factors which were significant in the waiting list outcome model included the centre at which a patient was registered and patient gender. The transplant centre will affect the outcome partly as a result of how different centres interpret

the assessment guidelines and partly due to the initial mix of patients that are referred to them; which will again influence the decisions they make in view of the assessment guidelines. Males were seen to experience death or removal sooner than females.

Several other patient, donor and transplant attributes were also significant in the post transplant model. Marginal livers used in transplantation (Section 1.5.3) are defined to be split or reduced livers, donors aged over 65 years old, and where the donor died due to infection. All these factors caused the times to post transplant events to be shorter. Identically matched donor and patient blood groups significantly improved post transplant survival, as did the covariate patient weight minus donor weight, implying that the patients who are heavier are more likely to experience better post transplant outcomes. This would be due to the heavier patients, actually being “healthier” than the lighter patients, due to the nature of liver diseases – in the latter stages of which, patients can lose a lot of weight.

7.4.3 Patient Progression

‘Can a simulation answer questions in the UK context about equity and utility within the transplant allocation and assessment process?’

It was possible to use Hepatica to capture and evaluate how different policies within the assessment and allocation processes affect the equity and utility within the liver transplantation system.

For evaluating the changes in the assessment rules, it was not possible to capture the patients that would join the waiting list as a direct result of changing the assessment rules, due to data limitations. However, changes in the assessment policies were mimicked by altering the pre-transplant prognosis of all the patients joining the waiting list. This in effect altered the patient mix joining the waiting list and thus the assessment rules in place.

The allocation rules were modelled directly in the simulation, by searching the waiting list for the most appropriate patient (according to the allocation rules in place), to identify the patient who should obtain the liver transplant.

The model is able to assess system equity and utility, resulting from various demand, supply, assessment rule, and allocation rule factors. This has helped to increase understanding of how various changes to assessment and allocation policies would affect the liver transplant system. By incorporating all patient groups, in particular super urgent patients, Hepatica is a more comprehensive model of the UK liver transplantation system than has previously been created.

7.5 Limitations and Further Work

Longer term it would be beneficial to develop an interface to make the simulation model more user friendly so that UK Transplant and the Liver Transplant Units can use it for testing various policies they may implement. More specific areas of further work are discussed below, which take forward the issues and limitations raised in Sections 7.3 and 7.4.

7.5.1 Suitable Measures to Enable Comparison Between Policies

Ranking and Balancing Outcome Measures

It became evident that there is no clear way in which to balance and rank the equity and utility measures against one another. The need for this is accentuated because when the demand for liver transplants is greater than the supply of livers there is no policy which optimises both the utility and equity within the system; either one can be improved, but generally only at the expense of the other. There is therefore a need for further development in determining the most appropriate equity and utility measures to use, and also the techniques used to rank and balance them.

The general public and doctors both have a high power and high interest in the liver transplant system, for example, the public have the power to refuse to donate, while the doctors have power in determining which patients should receive the donated livers. In order to develop the equity and utility measures further, input would be required from all the stakeholders in the liver transplantation process. Several studies have concluded that the general public have different views from doctors about the importance of equity and utility and how they should influence the allocation of liver transplants. Therefore, any approach which seeks to identify the core measures to consider, needs to involve the points of views of all sides.

There are many additional measures which could be used to assess the equity and utility of the system. Some of these were recorded from Hepatica, but only

a few key measures were used to compare different scenarios. There is scope to further develop how the scenarios are ranked which would allow the inclusion of additional measures. Multi-Criteria Decision Analysis could be employed here to rank equity and utility measures by importance (as defined by meeting with the various stakeholders), and then determine which policies result in the best outcomes.

Additional Outcome Measures

There are some measures commonly used within the healthcare setting which would aid the assessment and allocation decision processes. These include quality of life measures and the costs involved. There is also an ongoing debate about preventable diseases - should a more hard-line approach be taken, as the NHS shifts its focus towards preventing diseases and promotes leading healthier lifestyles.

An important utility measure commonly used in healthcare is Quality Adjusted Life Years (QALYs). To assess the overall gains in QALYs, the Quality of Life (QoL) patients experience will need evaluating at three stages:

- (1) On the waiting list;
- (2) Once transplanted; and
- (3) When the liver graft is rejected, and when a patients die due to other causes.

One of the measures that the NHS considers is the cost per QALY. This allows some comparison to be made between different treatments and provides a basis from which to prioritise treatments for different conditions (e.g., drug treatment

for high blood pressure or screening for cancer). The main limitation in the current liver transplant system is the shortage in the number of donors, and if a liver is donated then it will be used in transplantation. However, if a treatment is developed for end stage liver disease or the supply of donated livers increases, then costs will become more important (both the cost-effectiveness of liver transplants and the additional QALYs gained from a transplant).

Definition of Equity

The output from the simulation model showed that in general it is much harder to obtain equity in the system. The base scenario and alternative scenarios are biased towards or biased against transplanting certain patient groups. In particular, policies which prioritise super urgent patients give a much greater bias against routine patients. This is perfectly understandable and should be the case, as super urgent patients have a very short life expectancy without one. During the experimentation phase, one policy was developed to try and maximise equity within the system. Super urgent patients were no longer given priority and so a smaller number of them received a transplant, with the utility of the system undermined as a result. As further work it would be useful to change the definition of equity so that policies are allowed to allocate to super urgent patients where possible and then identify any biases against other patient groups (excluding the monitoring of all characteristics of super urgent patients).

Implications of New Developments

Healthcare in the UK is constantly evolving as a result of new developments and innovations, for example, the wider use of living liver transplants for adults on the NHS on the costs for and supply of liver transplants. Analytical methods need to be developed in order to capture their likely effect. If the use of living donors becomes more prevalent, any change in the donor's health would also need to be monitored when assessing the value of this alternative treatment. Cost-benefit analysis and the life years gained by the patient and any potential life years lost by the donor would be required.

Other future work may arise pending further technological developments. In particular, one study is showing promising signs in lengthening the time a liver can survive outside a human body (Gross 2007). This study could lead to further understanding of how the liver functions and therefore to new treatments of liver failure, similar to dialysis for kidney failure.

There is also some work to be done on establishing if education (on the causes of liver diseases and the likely outcomes, as well as, ways in which to prevent certain types of liver disease) is an effective means to reduce the number of end stage liver disease sufferers. This aspect is important due to the limited number of livers available.

Hepatica could easily be extended to incorporate these aspects, or could be used to give an early indication of the likely impact of any changes to demand and/or supply.

7.5.2 Estimating Events and Survival

Data Limitations

In order to improve the competing risks and survival models created it would be useful to be able to analyse data from a longer observation period. This would aid in confirming how patient survival changes over a longer period of time, especially important for estimating the long term benefits of a liver transplant. The models could also be calibrated with more recent data than for the years 1999-2002.

The logistic regression model developed to predict whether or not a patient joins the waiting list needs further development in order to be able to fully incorporate the assessment phase into the simulation model. To do this, further data needs to be collected from all the liver transplant units in the UK. This work would also need to capture how different decisions were made at the different liver transplant centres (i.e., how the fairly subjective assessment criteria and allocation rules are interpreted). This could be done by presenting several different patient waiting list and donation scenarios, from which it could be determined whether centres are likely to make the same decisions if they have similar patients mixes, or whether centres weight their decisions favouring either equity or utility.

As discussed in Section 7.4.2, the MELD score associated with the patients did not appear to be significant to the outcomes observed from the waiting list. The MELD score in our data set is only recorded at the time a patient joins the waiting list, however, the score is based on clinical measures which will change over time (as the disease progresses). Therefore, monitoring how the MELD score changes over time would help establish how ill a patient is, more accurately.

Models - Methodology and Assumptions

It was difficult to evaluate how well the survival and competing risks models fit the original data, since the models had many covariates. Taking the average values for the covariates leads to resulting distributions which would never occur. Notably, a number of binary variables are used which can only take the values 0 or 1. The “average” value that these variables took may be around 0.2 – which is meaningless. Separating the models by each combination of covariates, meant that very few data points existed to compare against. Another way to determine if the models are suitable would be by using re-sampling techniques to sample values from the models in the proportions based on the observed patient, donor and transplant characteristics, and comparing a Kaplan-Meier survival plot for the sampled cases with a Kaplan-Meier plot based on the original data.

There is also some work to be performed to identify whether the more complex competing risks model provides a better approximation to death or removal

outcomes than a simpler survival model would. Extra analysis would seek to confirm whether the extra effort in developing the more complicated model is justified (i.e., is able to capture the events and times more accurately).

7.5.3 Patient Progression

Assessment

There is a great deal of modelling work that could be done regarding the assessment process. One of the major areas of work would be to identify how the national assessment criteria are interpreted by the local liver transplant units.

Pre-Assessment Modelling

The model developed is limited to what is required for measuring the outcomes and meeting the objectives for modelling. Therefore, some aspects (in particular, prior to referral to the liver unit) were not modelled and the equity and utility measures are only considered in detail from when a patient joins the waiting list. However, as identified in Section 2.3.1, it is important that the system is equitable at all points in the system where decisions influence the progression of the patient to the next state. Geographical equity measures were analysed as patients joined the waiting list and are they received a transplant (Appendix G), however other patient attributes also require monitoring for equity purposes if a truly equitable system is to be identified.

Super Urgent Patients

In Chapter 5 we observed that a larger proportion of super urgent patients are transplanted within the base scenario in Hepatica, compared to the observed proportion within UK Transplant data. As a result, routine patients were having to wait longer for a transplant, with a greater number dying or being removed from the waiting list as a result.

The survival time analyses, for both pre- and post-transplant outcomes, did find significant differences between super urgent and routine patients, and this was captured within the covariates of the overall prediction model. However, the subsequent analysis performed within the simulation shows that the two groups of patients should be modelled separately.

More detailed information about the process of receiving and allocating a donated liver is required. Specifically, this needs to explore any factors (perhaps time or location) which prevent livers being allocated to a super urgent patient. It may be that additional states or assumptions are required within Hepatica to capture the progression of super urgent patients more accurately.

Optimal Timing

If utility became the most important aspect to consider then there would be a need to develop a model which identified the optimal time during the progression of a patient's disease at which to transplant. Much more work

would also be necessary to identify differences between the various diseases, and to identify the accuracy of the predictions.

7.6 Summary

The work presented in this thesis has illustrated the use of several different Operational Research and Statistical techniques for use in the modelling of the UK Liver Transplantation System. The techniques have aided in the further understanding of the assessment and allocation system currently implemented, and how changes to the current system may influence the overall equity and utility measures.

Hepatica includes new aspects which have either not been considered within the UK context and/or the various US models. These are:

- Modelling of both system equity and utility;
- The incorporation of super urgent patients; and
- Implementing a competing risks model to capture times to events from the waiting list.

Many of the limitations in the modelling are a result of the need to balance several aspects, common when modelling:

- (1) The level of detail to include in the model,
- (2) The complexity of the modelling technique implemented; and
- (3) Data limitations.

Thus, many ideas for further work have been generated. One important aspect in generalising the model so that the different liver transplant units may use it, would be to understand in more detail the decisions made at the different centres and the different patient mixes at each of the centres.

There are also many insights which have been gained into decision making within the UK Liver Transplantation System, which have been observed through the analysis performed. Firstly, there is a need to implement simple rules, and rules which change over time, to obtain the best equity and utility output measures. Secondly, it is easier to improve the overall utility in the system than the equity, due to the implications of prioritisation.

Appendix A

Patient and Donor Attribute Grouping

A.1 Disease Categories

A.1.1 UKT Disease Categories

The liver diseases which are recorded onto the UK Transplant database when a patient is registered onto the waiting list are listed in Table A.1 below.

Table A.1 Primary Liver Disease Codes as Recorded by UK Transplant.

Primary liver disease codes (at registration)			
400	Liver disease unknown	438	Drug (non-paracetamol)/toxin induced
410	Chronic liver failure cause unknown	439	FHF - other please specify
411	Primary biliary cirrhosis	440	Malignancy (ca) not classifiable
412	Autoimmune cirrhosis	441	Hepatocellular carcinoma non-cirrhotic
413	Post hepatitis b cirrhosis	442	Hepatocellular carcinoma cirrhotic
414	Sclerosing cholangitis	443	Cholangiocarcinoma
415	Alpha-1-antitrypsin deficiency	444	Primary liver sarcoma
416	Budd-chiari	445	Secondary liver tumour
417	Cryptogenic cirrhosis	446	Other mesenchymal tumours
418	Secondary biliary cirrhosis	447	Other hepatic malignancies
419	Alcoholic cirrhosis	448	Benign liver tumour
420	Biliary atresia	450	Metabolic disease
421	CLF - congenital hepatic fibrosis	460	Polycystic disease
422	Chronic Wilsons disease	461	Haemochromatosis
423	Congenital biliary disease	471	Acute rejection
424	Post hepatitis c cirrhosis	472	Chronic rejection
425	Cholestatic disease (paed)	473	Primary non-function
430	Acute hepatitis - unknown	474	Acute vascular occlusion
431	FHF - viral	475	Non thrombotic infarction
432	FHF - drug induced	476	Ductopenic rejection
433	FHF - toxin induced	477	Recurrent disease
434	Acute wilsons disease	478	Biliary complications
435	Acute hepatitis a	498	Other
436	Acute hepatitis b	499	Liver disease unknown
437	Drug induced - paracetamol	888	Not reported

A.1.2 Adjusted LAG Groupings

A study conducted by the Liver Advisory Group (Hudson *et al.* 2005), determined a set of disease groups which were relevant to combine. These *LAG groupings* were adjusted for this study, to help make the disease groups similar

in size and to maintain heterogeneous groups and are shown in Table A.2 below. Advice was taken from a Liver Disease Epidemiologist (Roderick 2004).

Table A.2 Disease Groupings Used within the Thesis.

Disease Grouping	Diseases Categories within the Grouping	
1 Other Cirrhotic Diseases (see categories 8 to 11)	- Primary biliary cirrhosis - Autoimmune cirrhosis	- Secondary biliary cirrhosis
2 Cholestatic Liver Disease	- Sclerosing cholangitis - Biliary atresia	- Congenital biliary disease - Cholestatic disease (paed)
3 Cancer	- Malignancy (ca) not classifiable - Hepatocellular carcinoma non-cirrhotic - Hepatocellular carcinoma cirrhotic - Cholangiocarcinoma	- Primary liver sarcoma - Secondary liver tumour - Other mesenchymal tumours - Other hepatic malignancies
4 Metabolic Liver Disease	- Alpha-1-antitrypsin deficiency - Chronic wilsons disease	- Metabolic disease - Haemochromatosis
5 Other Diagnosed Disease	- CLF - congenital hepatic fibrosis - Other	- Polycystic disease - Benign liver tumour
6 Super Urgent/Acute Liver Disease	- Budd-chiari - Acute hepatitis - unknown - FHF - viral - FHF - drug induced - FHF - toxin induced - Acute Wilsons disease - Acute hepatitis a - Acute hepatitis b - Drug induced - paracetamol - Drug (non-paracetamol)/toxin induced	- FHF - other please specify - Acute rejection - Chronic rejection - Primary non-function - Acute vascular occlusion - Non thrombotic infarction - Ductopenic rejection - Recurrent disease - Biliary complications
7 Unknown Liver Disease	Chronic liver failure cause unknown	- Liver disease unknown
8 Hepatitis B	- Post hepatitis b cirrhosis	
9 Cryptogenic Liver Disease	- Cryptogenic cirrhosis	
10 Alcoholic Liver Disease	- Alcoholic cirrhosis	
11 Hepatitis C	- Post hepatitis c cirrhosis	
12 Not Reported	- Not Reported	- Missing entries

A.2 Donor Cause of Death Groupings

Table A.3 below depicts how the donor causes of death were grouped, so that indicator variables could be created and used within the analysis. The groupings were made based on the advice from a Senior Lecturer of Public Health Medicine and Epidemiologist (Roderick 2004).

Table A.3 Donor Cause of Death Groupings Used within the Thesis.

Cause of Death Grouping	Causes of Death within the Grouping (as recorded by UK Transplant)
1 Intracranial	Intracranial Haemorrhage Intracranial Thrombosis Brain Tumour Hypoxic Brain Damage - All causes Intracranial - Type unclassified (CVA)
2 Trauma	Trauma - RTA - Car Trauma - RTA - Motorbike Trauma - RTA - Pushbike Trauma - RTA - Pedestrian Trauma - RTA - Unknown type Other Trauma - Suicide Other Trauma - Accident Other Trauma - Unknown cause Cardiac Arrest
3 Cardiovascular	Myocardial Infarction Aneurysm Ischaemic Heart Disease Cardiovascular - Type unclassified
4 Respiratory Failure	Pulmonary Embolism Pneumonia Asthma Respiratory Failure
5 Infections	Meningitis Septicaemia Infections - Type Unclassified
6 Other	Carbon Monoxide Poisoning Respiratory - Type Unclassified (Inc. Smoke Inhalation) Cancer, Other than Brain Tumour Paracetamol Overdose Other Drug Overdose (please specify) Other Unknown

A.3 Patient Model for End Stage Liver Disease (MELD) Score Groupings

The MELD score uses a mathematical formula based on serum creatinine, bilirubin, and INR. MELD scores can range from 6 (less ill) to 40 (gravely ill). MELD scores greater than 40 are all grouped together and receive a score of 40 (California Pacific Medical Centre). The individual score determines how urgently a patient needs a liver transplant within the next three months, for patients suffering from a chronic liver disease and is used in the USA to prioritise patients, as well as aiding in determining how frequently laboratory tests should be done. Table A.4 shows the values used to create the MELD score groups.

Table A.4 MELD Score Groupings Used within the Thesis.

MELD Grouping	Range of MELD Score	Frequency of Laboratory Test
1	≥ 25	Every 7 days
2	19-24	Every 30 days
3	11-18	Every 90 days
4	≤ 10	Every year

A.4 Patient Body Mass Index (BMI) Groupings

The Body Mass Index (BMI) is calculated using the following formula:

$$BMI = \frac{\text{weight (kg)}}{(\text{height (m)})^2}$$

Table A.5 shows how the patient BMI values were grouped in the analysis, using common definitions (World Health Organisation) of underweight, normal range, overweight and obese.

Table A.5 BMI Score Groupings Used within the Thesis.

BMI Grouping	Range of BMI Score
1 Underweight	< 18.50
2 Normal Range	18.50 - 24.99
3 Overweight	25.00 - 29.99
4 Obese	≥ 30.00

Appendix B

Definition of ABO-Compatibility

B.1 Definition

Once patients are on the waiting list they are in competition for the livers available. In the UK, a patient must have a compatible blood type (as depicted in Table B.1 below) to the donors (UKT Liver Advisory Group 1999).

Table B.1 ABO Blood Group Compatibility.

		Donor Blood Type			
		O	A	B	AB
Patient Blood Type	O	✓	✗	✗	✗
	A	✓	✓	✗	✗
	B	✓	✗	✓	✗
	AB	✓	✓	✓	✓

B.2 Patient and Donor Blood Group Distributions

Table B.2 shows the percentage by blood group: (1) of patients requiring liver transplant, and (2) of donors allocated to adult patients, between 1 January 1999 and 31 December 2002 (UK Transplant 1999-2002).

Table B.2 Proportions of Patients and Donors by Blood Group.

	Patients (%)	Donors (%)
O	45	52
A	40	38
B	11	8
AB	4	2

Appendix C

Coverage of UK Liver Transplant Units and UK Liver Units

Figure C.1 depicts the location of all the liver transplant units in the UK and the areas that each of the liver units retrieves livers from, as designated in 1993 (King's College Hospital). It can be observed that the South West of England does not have any liver transplant units. Patients and donors from this region are mainly the responsibility of Kings; however, other units including Birmingham may receive patients from this region for transplantation. There are a number of liver units (Table C.1) within the South West which can monitor patients, but these units are not able to provide liver transplant operations (British Liver Trust).



Figure C.1 Liver Retrieval Zones in the United Kingdom and Ireland.

Table C.1 Liver Units in the UK by Region (hospitals with liver transplant units are marked in bold).

Region	Hospital
East Anglia	Addenbrooke's , Cambridge
Mersey	Royal Liverpool Hospital, Liverpool
Mersey	University Hospital, Liverpool
N E Thames	Royal Free Hospital , London
N E Thames	Royal London Hospital, London
N E Thames	University College Hospital, London
N W Thames	St Mary's Hospital, London
Northern	Freeman Hospital , Newcastle Upon Tyne
North West	Manchester Royal Infirmary, Manchester
Oxford	John Radcliffe Hospital, Oxford
Oxford	Royal Berkshire Hospital, Reading
S E Thames	King's College Hospital , London
South West	Bristol Royal Infirmary, Bristol
South West	Derriford Hospital, Derriford Road, Plymouth
S W Thames	St George's Hospital, London
Trent	Royal Hallamshire Hospital, Sheffield
Trent	Queens Medical Centre, University Hospital, Nottingham
Wessex	Southampton General Hospital, Southampton
West Midlands	Queen Elizabeth Hospital , Birmingham
Yorkshire	St James' Hospital , Leeds
Aberdeen & Northern	Aberdeen Royal Infirmary, Aberdeen
Aberdeen & Northern	Ninewells Hospital, Dundee
Edinburgh & Lothian	Edinburgh Royal Infirmary , Edinburgh
Glasgow & W Scotland	Southern General Hospital, Glasgow
Glasgow & W Scotland	Glasgow Royal Infirmary, Glasgow
Glasgow & W Scotland	Gartnavel Hospital, Glasgow
Cardiff	Cardiff Liver Unit, University Hospital of Wales, Cardiff
Belfast	Royal Victoria Hospital, Belfast

Appendix D

The Kaplan-Meier Estimate

The Kaplan-Meier estimate (which provides a non-parametric estimate of the survival function) is normally used to analyse censored survival data. To obtain the Kaplan-Meier estimate a series of time intervals is constructed such that one death, D, is contained in a particular time interval and this death is taken to occur at the start of the interval. For example, suppose that $t_{(1)}$, $t_{(2)}$ and $t_{(3)}$ are 3 observed survival times, where $t_{(1)} < t_{(2)} < t_{(3)}$, and C is a censored survival time between $t_{(1)}$ and $t_{(2)}$. The intervals begin at $t_{(1)}$, $t_{(2)}$ and $t_{(3)}$. Note: more than one death may occur at the start of a particular interval.



Figure D.1 Constructing intervals, for deriving the Kaplan-Meier Estimate.

The Kaplan-Meier estimate of the survival function is given by:

$$\hat{S}(t) = \prod_{j=1}^k \left(\frac{n_j - d_j}{n_j} \right)$$

where n_j = the number of individuals who are alive just before time $t_{(j)}$
 (including those who are about to die at time $t_{(j)}$),

d_j = the number who die at time $t_{(j)}$,

k = the number of intervals.

The estimate is updated at the start of each of the intervals.

Example

Table D.1 gives the Kaplan-Meier estimates for the example depicted in Figure D.1.

Table D.1 Example of Calculating the Kaplan-Meier Estimate.

Time	n_j	d_j	$\hat{S}(t)$
$t_{(0)}$	7	0	1
$t_{(1)}$	7	2	$\frac{7-2}{7} = 0.714$
$t_{(2)}$	4	1	$\frac{7-2}{7} \times \frac{4-1}{4} = 0.536$
$t_{(3)}$	3	3	$\frac{7-2}{7} \times \frac{4-1}{4} \times \frac{3-3}{3} = 0$

Appendix E

Different Forms of Survival Function

Table E.1 Properties of Survival Functions with Different Underlying Hazards.

Model (Type)	Hazard Function			Computing Processing Time
	Model Assumptions	Modelled parametrically or non-parametrically?	Monotonic or non-monotonic functions	
Cox Regression (PH)	Hazard functions are proportional, e.g. patient A will always be α times more likely to die than patient B.	Baseline hazard function modelled non-parametrically.	Any, as defined non-parametrically (not restricted to unimodal).	Non-parametric distributions require greater computer processing time.
Exponential (PH)	Hazard functions are proportional, e.g. patient A will always be α times more likely to die than patient B.	Exponential distribution used to model baseline hazard.	Monotonic Function.	Parametric therefore less computer processing time.
Weibull (PH)	Hazard functions are proportional, e.g. patient A will always be α times more likely to die than patient B. [Can be re-parameterised as an AFT model].	Weibull distribution used to model baseline hazard.	Monotonic Function.	Parametric therefore less computer processing time.
Log-Logistic (AFT)	The shape of the survival curve is the same for all patients, but they move along it faster or slower according to the value of their covariates.	Log-Logistic distribution used to model baseline hazard.	Unimodal.	Parametric therefore less computer processing time.
Lognormal (AFT)	The shape of the survival curve is the same for all patients, but they move along it faster or slower according to the value of their covariates.	Lognormal distribution used to model baseline hazard.	Unimodal.	Similar to log-logistic but its usefulness is limited as it can only be expressed in terms of integrals. Therefore, requires greater computer processing time/more complex calculation algorithm.

Appendix F

Allocation Rule Details

L1 Old Base Allocation Rules

Base Scenario (in operation until July 2006).

- | | | | |
|----------------------------------------------------|-----------|-----------|---------|
| 1] local compatible SU patient | | | |
| O → O, B | A → A, AB | B → B, AB | AB → AB |
| 2] national compatible SU patient | | | |
| O → O, B | A → A, AB | B → B, AB | AB → AB |
| 3] local compatible routine patient | | | |
| O → O, B | A → A, AB | B → B, AB | AB → AB |
| 4] national compatible routine patient | | | |
| O → O, B | A → A, AB | B → B, AB | AB → AB |
| 5] local compatible SU patient (O → A, AB) | | | |
| 6] national compatible SU patient (O → A, AB) | | | |
| 7] local compatible routine patient (O → A, AB) | | | |
| 8] national compatible routine patient (O → A, AB) | | | |
| 9] local non compatible | | | |
| 10] national non compatible | | | |

L2 Current Base Allocation Rules

Current Scenario (in operation from July 2006) - based on the information presented by Hamilton and O'Neill (2006), as explained further in Section 3.3.4.

- | | | | |
|-------------------------------------------------------|-----------|-----------|---------|
| 1] local compatible SU patient | | | |
| O → O | A → A, AB | B → B, AB | AB → AB |
| 2] national compatible SU patient | | | |
| O → O | A → A, AB | B → B, AB | AB → AB |
| 3] local compatible routine patient | | | |
| O → O | A → A, AB | B → B, AB | AB → AB |
| 4] national compatible routine patient | | | |
| O → O | A → A, AB | B → B, AB | AB → AB |
| 5] local compatible SU patient (O → A, B, AB) | | | |
| 6] national compatible SU patient (O → A, B, AB) | | | |
| 7] local compatible routine patient (O → A, B, AB) | | | |
| 8] national compatible routine patient (O → A, B, AB) | | | |
| 9] local non compatible | | | |
| 10] national non compatible | | | |

L3 Priority Given to Patients with any Compatible Blood Group to the Donor

Factor L3 will follow the same rules as before in that the priority order will be to allocate to patients with a compatible blood group to the donors', to super urgent patients and to patients from the centre associated to the retrieval area in which the donor fell. However, unlike the compatibility rules in place currently, patients with blood group O will not be given priority for livers donated by blood group O donors.

- 1] local compatible SU patient
 $O \rightarrow O, A, B, AB$ $A \rightarrow A, AB$ $B \rightarrow B, AB$ $AB \rightarrow AB$
- 2] national compatible SU patient
 $O \rightarrow O, A, B, AB$ $A \rightarrow A, AB$ $B \rightarrow B, AB$ $AB \rightarrow AB$
- 3] local compatible routine patient
 $O \rightarrow O, A, B, AB$ $A \rightarrow A, AB$ $B \rightarrow B, AB$ $AB \rightarrow AB$
- 4] national compatible routine patient
 $O \rightarrow O, A, B, AB$ $A \rightarrow A, AB$ $B \rightarrow B, AB$ $AB \rightarrow AB$
- 5] local non compatible
- 6] national non compatible

L4 Priority Given to Patients with an Identical Blood Group to the Donor

Factor L4 will allocate first to patients with identical blood groups to the donor, then to patients with compatible blood groups to the donor. It will also prioritise by transplant urgency and retrieval centre.

- 1] local identical SU patient
 $O \rightarrow O$ $A \rightarrow A$ $B \rightarrow B$ $AB \rightarrow AB$
- 2] national identical SU patient
 $O \rightarrow O$ $A \rightarrow A$ $B \rightarrow B$ $AB \rightarrow AB$
- 3] local identical routine patient
 $O \rightarrow O$ $A \rightarrow A$ $B \rightarrow B$ $AB \rightarrow AB$
- 4] national identical routine patient
 $O \rightarrow O$ $A \rightarrow A$ $B \rightarrow B$ $AB \rightarrow AB$
- 5] local compatible SU patient
 $O \rightarrow A, B, AB$ $A \rightarrow AB$ $B \rightarrow AB$
- 6] national compatible SU patient
 $O \rightarrow A, B, AB$ $A \rightarrow AB$ $B \rightarrow AB$
- 7] local compatible routine patient
 $O \rightarrow A, B, AB$ $A \rightarrow AB$ $B \rightarrow AB$
- 8] national compatible routine patient
 $O \rightarrow A, B, AB$ $A \rightarrow AB$ $B \rightarrow AB$
- 9] local non compatible
- 10] national non compatible

L5 Priority Given to Patients in the Same Centre Where Donated Liver is Retrieved

Factor L5 will assume the same blood group compatibility rules as the current allocation rules. It will then give priority to patients within the same centre as where the donated liver is retrieved, then to SU patients.

- 1] local compatible SU patient
 $O \rightarrow O$ $A \rightarrow A, AB$ $B \rightarrow B, AB$ $AB \rightarrow AB$
- 2] local compatible routine patient
 $O \rightarrow O$ $A \rightarrow A, AB$ $B \rightarrow B, AB$ $AB \rightarrow AB$
- 3] local compatible SU patient ($O \rightarrow A, B, AB$)
- 4] local compatible routine patient ($O \rightarrow A, B, AB$)
- 5] national compatible SU patient
 $O \rightarrow O$ $A \rightarrow A, AB$ $B \rightarrow B, AB$ $AB \rightarrow AB$
- 6] national compatible routine patient
 $O \rightarrow O$ $A \rightarrow A, AB$ $B \rightarrow B, AB$ $AB \rightarrow AB$
- 7] national compatible SU patient ($O \rightarrow A, B, AB$)
- 8] national compatible routine patient ($O \rightarrow A, B, AB$)
- 9] local non compatible
- 10] national non compatible

L6 No Priority Given to Patients from the Retrieving Centre

Factor L6 considers all allocations on a national basis, i.e., does not factor in a priority for the retrieving centre.

- 1] compatible SU patient
 $O \rightarrow O$ $A \rightarrow A, AB$ $B \rightarrow B, AB$ $AB \rightarrow AB$
- 2] compatible routine patient
 $O \rightarrow O$ $A \rightarrow A, AB$ $B \rightarrow B, AB$ $AB \rightarrow AB$
- 3] compatible SU patient ($O \rightarrow A, B, AB$)
- 4] compatible routine patient ($O \rightarrow A, B, AB$)
- 5] non compatible

L7 Priority Given to Patients registered for their first transplant

Factor L7 will use the current compatibility rules and then prioritise patients who are waiting for their first liver transplant above those not waiting for their first liver transplant.

- 1] compatible requiring a first transplant
 $O \rightarrow O$ $A \rightarrow A, AB$ $B \rightarrow B, AB$ $AB \rightarrow AB$
- 2] compatible requiring a first transplant ($O \rightarrow A, B, AB$)
- 3] compatible not requiring a first transplant
 $O \rightarrow O$ $A \rightarrow A, AB$ $B \rightarrow B, AB$ $AB \rightarrow AB$
- 4] compatible not requiring a first transplant ($O \rightarrow A, B, AB$)
- 5] non compatible requiring a first transplant
- 6] non compatible not requiring a first transplant

L8 Priority Given to Patients registered for a successive transplant

Factor L8 will use the current compatibility rules and then prioritise patients who are waiting for their successive liver transplant above those that are waiting for their first liver transplant.

- 1] compatible not requiring a first transplant
 $O \rightarrow O$ $A \rightarrow A, AB$ $B \rightarrow B, AB$ $AB \rightarrow AB$
- 2] compatible not requiring a first transplant ($O \rightarrow A, B, AB$)
- 3] compatible requiring a first transplant
 $O \rightarrow O$ $A \rightarrow A, AB$ $B \rightarrow B, AB$ $AB \rightarrow AB$
- 4] compatible requiring a first transplant ($O \rightarrow A, B, AB$)
- 5] non compatible not requiring a first transplant
- 6] non compatible requiring a first transplant

L9 Priority Given to Younger Patients

Factor L9 will give priority to the youngest patients with compatible blood groups.

- 1] youngest compatible patient
 $O \rightarrow O$ $A \rightarrow A, AB$ $B \rightarrow B, AB$ $AB \rightarrow AB$
- 2] youngest compatible patient ($O \rightarrow A, B, AB$)
- 3] youngest non compatible

L10 Priority Given to Older Patients

Factor L10 will give priority to the oldest patients with compatible blood groups.

- 1] eldest compatible patient
 $O \rightarrow O$ $A \rightarrow A, AB$ $B \rightarrow B, AB$ $AB \rightarrow AB$
- 2] eldest compatible patient ($O \rightarrow A, B, AB$)
- 3] eldest non compatible

L11 Priority Given to Patients who have been waiting the shortest time

Factor L11 will give priority to the patients who have compatible blood groups to the donor and have been waiting the shortest time.

- 1] waiting the shortest time and compatible
 $O \rightarrow O$ $A \rightarrow A, AB$ $B \rightarrow B, AB$ $AB \rightarrow AB$
- 2] waiting the shortest time and compatible ($O \rightarrow A, B, AB$)
- 3] non compatible waiting the shortest time

L12 Priority Given to Patients who have been waiting the longest time

Factor L12 will give priority to the patients who have compatible blood groups to the donor and have been waiting the longest time.

- 1] waiting the longest time and compatible
 $O \rightarrow O$ $A \rightarrow A, AB$ $B \rightarrow B, AB$ $AB \rightarrow AB$
- 2] waiting the longest time and compatible ($O \rightarrow A, B, AB$)
- 3] non compatible waiting the longest time

L13 Priority Given to Patients where the absolute difference between donor and patient weight is minimised

Factor L13 will give priority to patients with compatible blood groups to the donor and where the absolute difference between donor weight and patient weight is minimised.

- 1] min(absolute(donor weight-recipient weight)) and compatible
 $O \rightarrow O$ $A \rightarrow A, AB$ $B \rightarrow B, AB$ $AB \rightarrow AB$
- 2] min(absolute(donor weight-recipient weight)) and compatible ($O \rightarrow A, B, AB$)
- 3] min(absolute(donor weight-recipient weight)) and non compatible

L14 Priority Given to Patients with the soonest Death or Removal time (i.e., worst pre-transplant prognosis)

Factor L14 will give priority to patients with compatible blood groups to the donor and by the patient who will next die or be removed from the waiting list.

- 1] next DR time and compatible
 $O \rightarrow O$ $A \rightarrow A, AB$ $B \rightarrow B, AB$ $AB \rightarrow AB$
- 2] next DR time and compatible ($O \rightarrow A, B, AB$)
- 3] next DR time and non compatible

L15 Priority Given to Patients with the best prognosis post transplant

Factor L15 will give priority to patients with compatible blood groups to the donor and by the patient who will gain the most days post transplant, if they were to be transplanted with the current liver.

- 1] furthest DGFRL time and compatible
 $O \rightarrow O$ $A \rightarrow A, AB$ $B \rightarrow B, AB$ $AB \rightarrow AB$
- 2] furthest DGFRL time and compatible ($O \rightarrow A, B, AB$)
- 3] furthest DGFRL time and non compatible

L16 Priority Given to Patients with best prognosis compared to expected prognosis without a transplant

Factor L16 will give priority to patients with compatible blood groups to the donor and by the patient who will gain the most days post transplant compared to how long they are currently expected to live, if they were to be transplanted with the current liver.

- 1] max(DGFRL time - DR time) and compatible
 $O \rightarrow O$ $A \rightarrow A, AB$ $B \rightarrow B, AB$ $AB \rightarrow AB$
- 2] max(DGFRL time - DR time) and compatible ($O \rightarrow A, B, AB$)
- 3] max(DGFRL time - DR time) and non compatible

L17 An adaptive policy which attempts to make allocation decisions through keeping track of equity measures, for groups not fairly transplanted across, within the other allocation policies

Factor L17 will aim to give the fairest equity measures and hence decide on a transplant by means to assessing the current equity figures. It will also make sure that only compatible transplants can take place.

- 1] compatible patient and when % transplant in a particular group is lower than rest
 $O \rightarrow O, A, B, AB \rightarrow A, AB$ $B \rightarrow B, AB$ $AB \rightarrow AB$
- 2] non compatible patient and when % transplant in a particular group is lower than rest

Appendix G

Geographical Equity Results

This appendix summarises the results from two studies which consider the geographical equity between different patient groups requiring liver transplantation. The first (Section G.1) performed by Suchi Patel considered all the patients that were referred to Birmingham Liver Unit for potential assessment for liver transplantation (with an initial appointment at Birmingham Liver Unit (BLU) between 1/1/99 and 31/12/02, and outcomes as recorded by July 2004). The second (Section G.2) was performed by Dr Paul Roderick and considered the patients that joined the UKT waiting list from 1/1/00 to 31/12/02, and the outcomes as recorded on the National Transplant Database as at 7/7/03. These analyses helped to assess if certain areas of the UK were accessing significantly fewer liver transplants than they should be (equity by location).

G.1 Geographic Comparisons of Referrals to BLU

Figure G.1 summarises the eventual outcomes of all 765 patients referred to BLU.

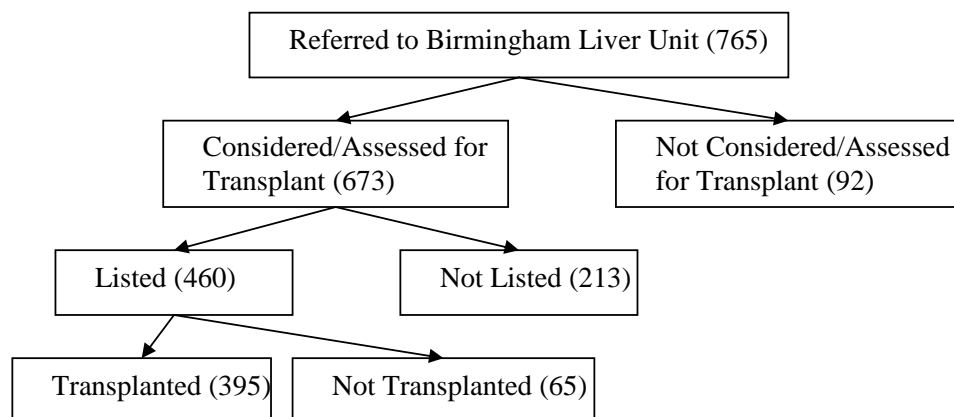


Figure G.1 A tree diagram to represent the decision based outcomes that were experienced, after referral to Birmingham Liver Unit.

The patients that are in the referred category but are not considered for transplant, were inpatients that visited Birmingham and had a diagnosis that could have potentially benefited from transplant (identified by matching the patient diagnoses with the list of transplantable disease, as in Table A.1 Appendix A).

G.1.1 Methodology

Sections G.1.2-G.1.12 present the findings of the analysis which considered geographical equity for the outcomes: (1) to assessment, and (2) to listing, across the patients groups: (1) transplant urgency, (2) age at first visit, and (3) primary liver disease. Analysis is also performed to assess if there are differences between the time a patient comes for their first visit to the liver unit: (1) to the time of their assessment, and (2) to the time of listing on to the waiting list.

The patient's location was defined as within the Birmingham Retrieval Area and outside of the Birmingham Retrieval Area. The chi-squared statistic is calculated to identify differences within the numbers (as presented in Sections G.1.2-G.1.12). A map of the English Strategic Health Authorities (post April 2002), Health Authorities of Wales, Scotland and Northern Ireland was also created using data obtained from the Edina website, UKBorders (Edina), and this map is used to present various rates by Strategic Health Authorities (SHA) and Health Authorities (HA), as present in 2001. All the analysis is performed and presented using ArcGIS, MS Excel, and Jasc Paint Shop Pro software. The grey areas on the maps show regions from where no referrals were made to Birmingham liver unit for the purposes of liver transplantation, between 01/01/99 and 31/12/02 (UK Transplant 1999-2002).

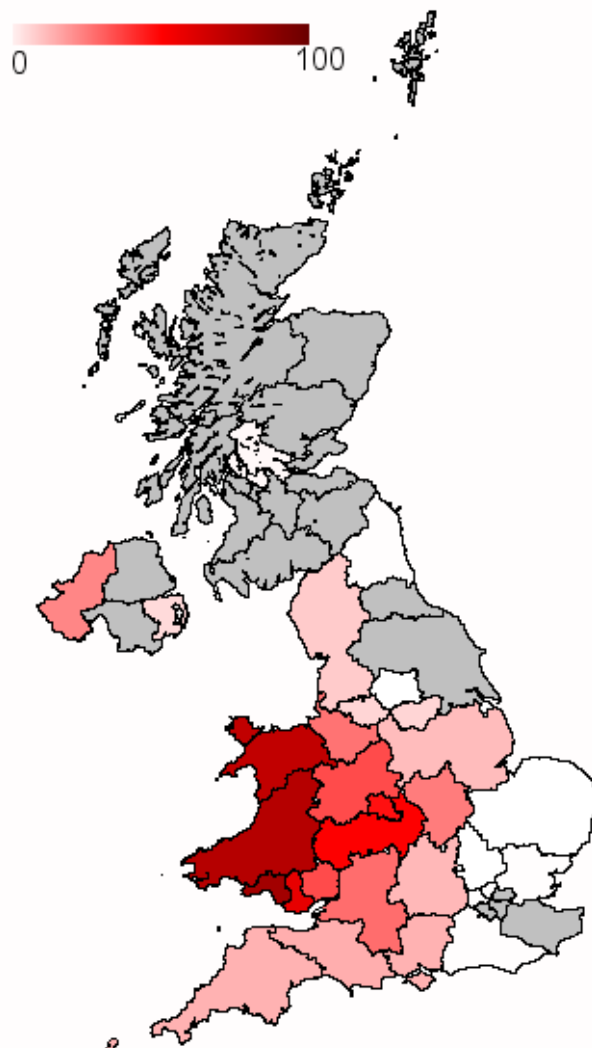
Annex 1 shows the number of referrals from and the population of each region, and the referral rates per 1,000,000 population. Note that the population figures (General Register Office for Scotland (2003); Isle of Man Government (2001);

Northern Ireland Statistics and Research Agency (2002); Office for National Statistics (2002); States of Jersey (2002); Welsh Assembly Government (Llywodraeth Cynulliad Cymrn) (2001)) had to come from various different sources and that a referral rate for the “Abroad” grouping was not attained since it was deemed incomparable.

G.1.2 Referral Rates by location

Table G.1 Referral rates to BLU by retrieval area

	Birmingham Region	Outside the Birmingham Region
Total Population	10,068,618	32,143,970
Number of Referrals	421	344
Expected Number of Referrals under H_0	175	559
Chi-squared test	P value	<0.01



By comparing Figure G.2 with Figure C.1 in Appendix C, it can be seen that, as would be expected, the higher referring units are within the area Birmingham serves. The numbers were statistically significantly different (Table G.1).

Northern Ireland (which is within the area covered by BLU) seems to have fewer referrals than might be expected, when comparing to the other regions that BLU serves. The numbers

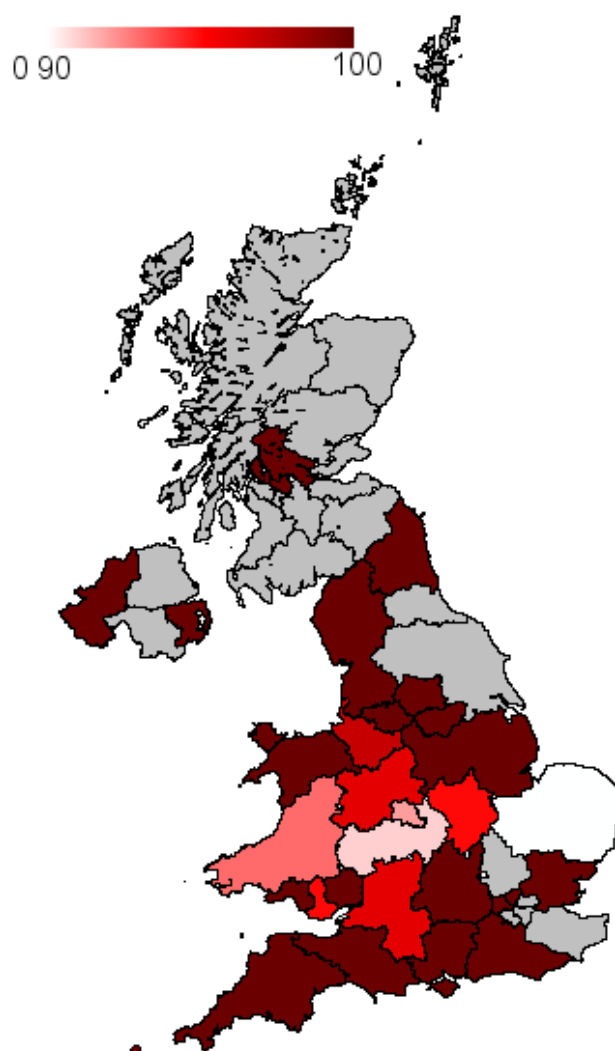
Figure G.2 Referral rates to BLU for each of the SHAs of England, and HAs of Wales, Northern Ireland and

Scotland, per 1,000,000 residents

G.1.3 Assessed (of Referrals) by location

Table G.2 Number of Patients Assessed of Those Referred to BLU by retrieval area.

	Birmingham Region	Outside the Birmingham Region
Number of Referrals	421	344
Number Assessed	366	307
Expected Number to be Assessed under H_0	370	303
Chi-squared test	P value	0.73



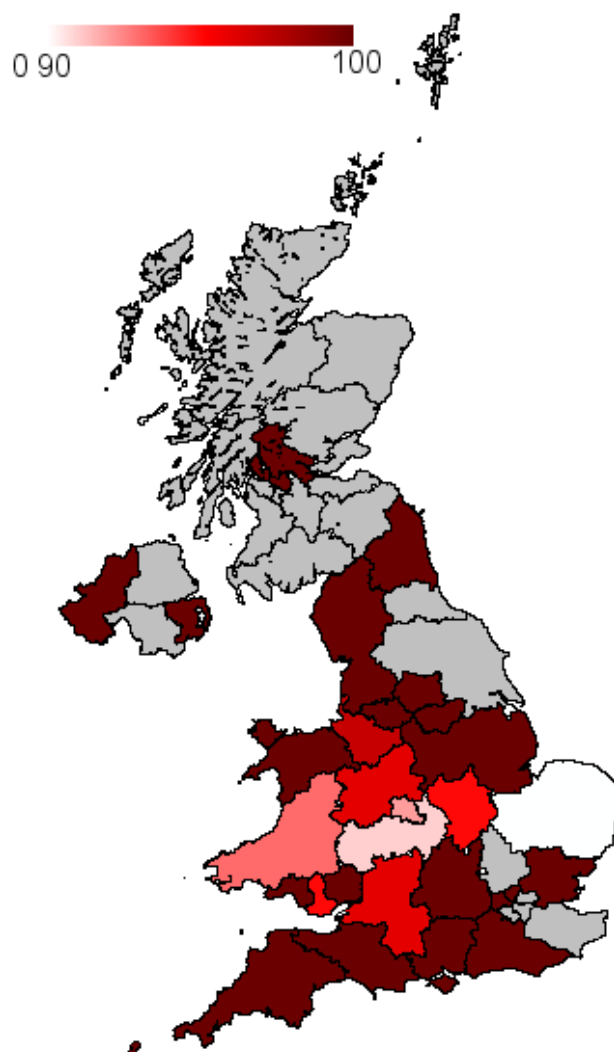
The map indicates that for many regions outside of the Birmingham Liver Unit area had 100% of referrals, assessed for transplantation. However, the regions within the Birmingham Liver Unit area had 91-100% of their referrals assessed. Statistically the difference is not significant (Table G.2).

Figure G.3 Percentage of patients referred to Birmingham Liver Unit that were assessed, by the SHAs of England, and HAS of Wales, Northern Ireland and Scotland

G.1.4 Listed (of Referrals) by location

Table G.3 Number of Patients Listed of Those Referred to BLU by retrieval area.

	Birmingham Region	Outside the Birmingham Region
Number of Referrals	421	344
Number Listed	250	210
Expected Number to be listed under H_0	253	207
Chi-squared test	P value	0.77



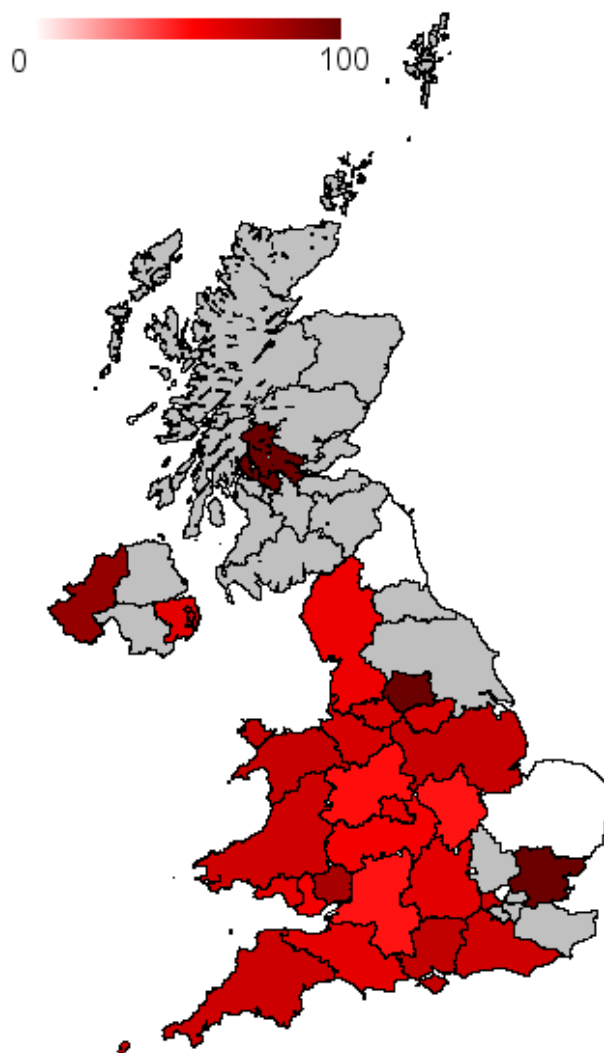
From Figure G.4 we can see that the SHAs and HAs which border “Birmingham and the Black Country” have a slightly smaller proportion of referrals placed on the waiting list. However, this was not significant (Table G.3).

Figure G.4 Percentages of those referred to Birmingham Liver Unit that were placed on the waiting list, by the SHAs of England, and HAs of Wales, Northern Ireland and Scotland

G.1.5 Listed (of Assessed) by location

Table G.4 Number of Patients Listed of Those Assessed at BLU by retrieval area.

	Birmingham Region	Outside the Birmingham Region
Number Assessed	366	307
Number Listed	250	210
Expected Number to be Listed under H_0	250	210
Chi-squared test	P value	0.99



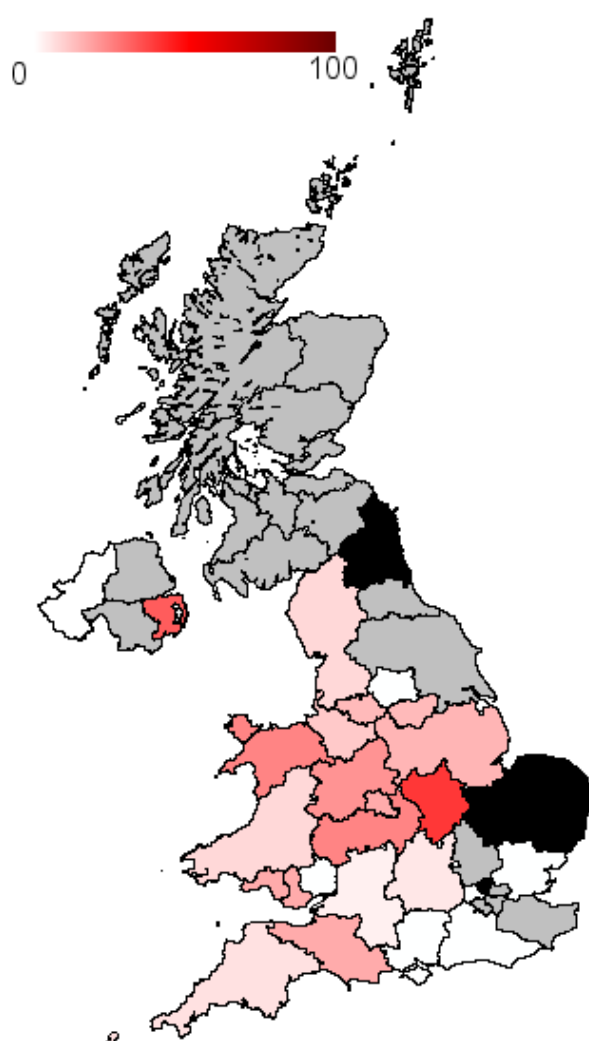
From Figure G.5 we cannot see a pattern emerging for the proportions of those assessed that were placed on to the waiting list, and the tests in Table G.4 confirm that there are no differences in the chance of being listed.

Figure G.5 Percentage of patients assessed at Birmingham Liver Unit that were placed on the WL, by the SHAs of England, and HAs of Wales, Northern Ireland and Scotland

G.1.6 Referrals by Transplant Urgency and location

Table G.5 Number of Referrals by Transplant Urgency and retrieval area.

	Birmingham Region	Outside the Birmingham Region
Number Listed	250	210
Number Super Urgent	44	22
Expected Number of Super Urgent patients under H_0	36	30
Chi-squared test	P value	0.04



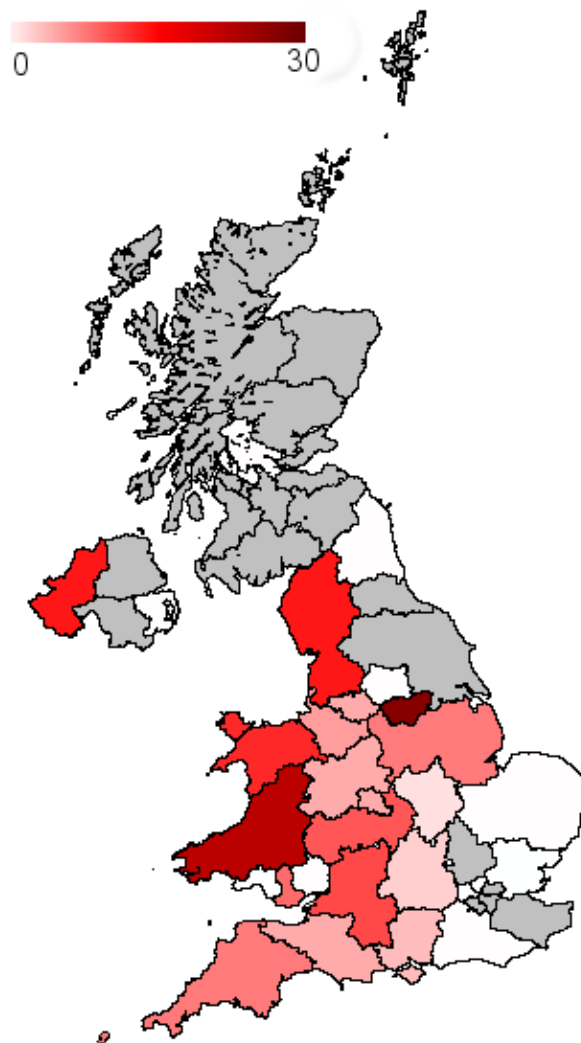
From Figure G.6 it can be seen that greater proportions of super urgent patients were referred from the regions around Birmingham, than the proportions referred from further away, and this is found to be statistically significant (Table G.5).

Figure G.6 Percentage of patients referred to Birmingham Liver Unit that were of super urgent status when assessed, by the SHAs of England, and HAs of Wales, Northern Ireland and Scotland

G.1.7 Referrals by Patient Age and location

Table G.6 Number of Referrals by Patient Age and retrieval area.

	Birmingham Region	Outside the Birmingham Region
Number of Referrals	421	344
Number greater than 65 years old	31	25
Expected Number of patients greater than 65 years old under H_0	31	25
Chi-squared test	P value	0.96



The map shows little difference between the proportion of patients aged 66 and older referred from the regions around Birmingham, and the proportion referred from further away. Statistical tests also demonstrate no significant difference (Table G.6).

Figure G.7 Percentage of patients referred to Birmingham Liver Unit that were between 66 years or older at their first appointment, by the SHAs of England, and HAs of Wales, Northern Ireland and Scotland

G.1.8 Referrals by Disease and Location

The LAG disease groupings (Hudson *et al.* 2004) were used to evaluate whether the mix of patient diseases differed by region.

Table G.7 Number of referrals and disease diagnoses by region.

Region	Number of Referrals	Number of different disease diagnoses
Abroad	31	8
Birmingham and IoM (B & IoM)	421	37
Cambridge (C)	80	21
Edinburgh (E & AB)	2	2
Kings and Jersey (K & J)	172	20
Leeds (L)	34	10
Newcastle (N)	22	11
Royal Free (RF)	3	2

Table G.7 shows that the variety of diseases that are referred from the local region is greater than from further away. However, this will be due partly to the larger number of cases referred from nearby.

Table G.8 Contingency table of all regions by all LAG groupings.

	B & IoM	C	E & AB	K & J	L	N	RF	Grand Total
Cirrhotic	285	52	30	123	25	16	3	534
Cholestatic	29	6	1	25	3	2		66
Cancers	1	1						2
Metabolics	9			3	2			14
Others/Not Reported/Unknown	76	13	1	19	1	3		107
Super-Urgent/Acute	21	8	1	2	3	1		36
	421	80	33	172	34	22	3	765

A Chi-Squared test performed on a grouped version of Table G.8 (to account for any cells with expected values less than 5) returned a p-value of 0.000041. This means that the disease groups that are referred to Birmingham from the various areas are significantly different in their distribution.

G.1.9 Time from First Visit to Assessment by Location

Table G.9 Time from first visit to assessment

	Time to assessment
Birmingham Area	
Mean time	114
N	366
Variance	58111
Not Birmingham Area	
Mean time	103
N	307
Variance	47997
Difference between means test	
Z value	0.6197
P value	0.2324

The results in Table G.9 show that there is no significant difference between the time from the first appointment to the time of the assessment, between the groups Birmingham and Not Birmingham.

G.1.10 Time from first visit to listing by location

Table G.10 Time from first visit to listing

	Time to listing
Birmingham Area	
Mean time	167
N	250
Variance	70266
Not Birmingham Area	
Mean time	167
N	210
Variance	75089
Difference between means test	
Z value	0
P value	0.5

The results in Table G.10 show that there is no significant difference between the time from the first appointment to the time of listing on to the waiting list, between the groups Birmingham and Not Birmingham.

G.1.11 Reasons for Patients not being Listed

This section identifies that there were no differences by location in the reasons why patients were not listed. Three reasons are considered: the patient was too well (Table G.11), the patient was too ill or died during assessment (Table G.12), and the patient would not recover post transplant (Table G.13).

Table G.11 Results from testing the hypothesis that no difference exists between the proportions of patients considered too well for transplantation, within the Birmingham area and outside this area.

	Birmingham Region	Outside the Birmingham Region
Number not listed	146	123
Number too well	28	23
Expected Number of patients too well for transplant under H_0	28	23
Chi-squared test	P value	0.93

Table G.12 Results from testing the hypothesis that no difference exists between the proportions of patients considered too ill or that died during assessment, within the Birmingham area and outside this area.

	Birmingham Region	Outside the Birmingham Region
Number not listed	146	123
Number too ill/died during assessment	43	36
Expected Number of patients too ill/died during assessment for transplant under H_0	43	36
Chi-squared test	P value	0.98

Table G.13 Results from testing the hypothesis that no difference exists between the proportions of patients considered too high risk for transplant, within the Birmingham area and outside this area.

	Birmingham Region	Outside the Birmingham Region
Number not listed	146	123
Number too considered high risk for transplant	7	7
Expected Number patients considered too high risk for transplant under H_0	8	6
Chi-squared test	P value	0.75

G.1.12 Conclusions and Limitations

Conclusions

The main findings of the analysis presented are that once patients are referred to Birmingham Liver Unit, location is not a factor in whether a patient is placed onto the waiting list or not; the attributes age and urgency status by location also do not affect a patients' chances of obtaining a liver transplant once referred.

It has also been shown that more referrals come from within the Birmingham Retrieval Zone which is to be expected since patients farther away will be referred to other Liver Units. There is also a tendency for a higher proportion of super urgent patients to be referred from within the Birmingham Retrieval Zone.

More disease types are represented by the referrals from within the Birmingham area. Fewer types of disease diagnoses are represented from regions further away.

This implies that location equity is met and that patients are equally likely to progress through the stages at Birmingham Liver Unit, wherever they are referred from.

Limitations

The main limitation of this analysis is that the data considered is from only one liver unit. This means that none of the hypothesis can be generalised across all the liver transplant units.

Also, it was very difficult to find a single reference which gave the population figures for all regions considered at one single time point. Instead several references had to be consulted and the figures range from 2001 to 2003. This does not quite match the time period of the Birmingham data, which went from 1999 to 2002.

G.2 Equity of Listing by Geography

Roderick's (2003) analysis considered all the patients who joined the UK Transplant waiting list. Tests were performed to identify if the registration rates were significantly different by age band, gender, and location (SHA). The analysis showed no significant differences in the number of referrals from the different regions, or the other factors. However, this analysis does assume that there will be a similar mix of patients requiring liver transplants, across the UK.

Annex 1 to Appendix G

A list of all the regions, with the number of referrals, population, and the referral rate per 1,000,000 population.

Region	Number of referrals	Total population	Referrals per 1,000,000 population
<i>English Strategic Health Authorities</i>			
Avon, Gloucestershire and Wiltshire	64	2145000	30
<i>Birmingham and the Black Country</i>	110	2253000	49
<i>Cheshire & Merseyside</i>	68	2343000	29
<i>Coventry, Warwickshire, Herefordshire and Worcester</i>	80	1522000	53
Cumbria and Lancashire	21	1900000	11
Dorset and Somerset	20	1184000	17
Essex	1	1612000	1
Greater Manchester	22	2482000	9
Hampshire and Isle of Wight	28	1749000	16
Leicestershire, Northamptonshire and Rutland	42	1550000	27
Norfolk, Suffolk and Cambridgeshire	1	2138000	0
North Central London	1	1179000	1
North West London	1	1729000	1
Northumberland, Tyne & Wear	1	1382000	1
<i>Shropshire and Staffordshire</i>	55	1482000	37
South West Peninsula	25	1562000	16
South Yorkshire	11	1265000	9
Surrey and Sussex	3	2548000	1
Thames Valley	31	2076000	15
Trent	37	2611000	14
West Yorkshire	1	2078000	0
<i>Northern Ireland</i>			
<i>Eastern Northern Ireland</i>	5	665726	8
<i>Western Northern Ireland</i>	7	284877	25
<i>Scotland</i>			
Greater Glasgow	2	866370	2
<i>Wales</i>			
<i>Bro Taf</i>	22	366800	60
<i>Dyfed Powys</i>	18	236300	76
<i>Gwent</i>	10	273500	37
<i>Morgannwg</i>	20	245000	82
<i>North Wales</i>	23	320100	72
<i>Other</i>			
<i>Isle of Man</i>	3	76315	39
Jersey	1	87600	11
Foreign	31	N/A	N/A

Those in italic and bold are within the Birmingham Retrieval Zone.

Appendix H

Cox-Snell Residuals

The residual most commonly used in the analysis of survival data is the Cox-Snell Residual, r_{C_i} . The way in which to calculate Cox-Snell residuals is dependent on the underlying distribution survival times being considered.

The general form of the Cox-Snell residual, for the i^{th} individual is:

$$r_{C_i} = \hat{H}_i(t_i) = -\log \hat{S}_i(t_i)$$

where $\hat{H}_i(t_i)$ is the estimated cumulative hazard function,
 $\hat{S}_i(t_i)$ is the estimated survivor function.

The Cox-Snell Residuals for the Weibull Distribution are then:

$$r_{C_i} = \exp(r_{S_i})$$

The Cox-Snell Residuals for the Loglogistic Distribution are then:

$$r_{C_i} = \ln\{1 + \exp(r_{S_i})\}$$

The Cox-Snell Residuals for the Lognormal Distribution are then:

$$r_{C_i} = -\ln\{1 - \Phi(r_{S_i})\}$$

where

$r_{S_i} = \{\log t_i - \hat{\mu} - \hat{\alpha}_1 x_{1i} - \hat{\alpha}_2 x_{2i} - \dots - \hat{\alpha}_p x_{pi}\} / \hat{\sigma}$ = the standardised residual

where

t_i is the observed survival time for patient i ,

$\hat{\mu}$ estimated mean of the data,

$\hat{\alpha}_j$ estimated coefficient of variable j ,

x_{ji} value of variable j for patient i ,

$\hat{\sigma}$ estimated standard deviation of the data.

To be a reasonable fit, the r_{C_i} should have a unit exponential distribution. This can be tested for by plotting $-\ln \hat{S}(r_{C_i})$ against r_{C_i} , where $\hat{S}(r_{C_i})$ is the Kaplan-Meier Estimate of the survival function of the Cox-Snell Residuals. If the fit is reasonable this plot should show a straight line with gradient 1 and which passes through the origin.

This can help us to find the most appropriate model for each transition. To analyse the appropriateness of the model, i.e., how closely the model fits to the data, the residuals have to be analysed. Plots of the actual data and the fitted model are also helpful in visualising the fit.

Appendix I

Logistic Regression Models to Capture the Outcomes from Referral

I.1 Introduction

Logistic regression models were developed to capture the decision of whether to list a patient onto the waiting list or not, using the data from Birmingham Liver Unit (BLU). The covariates used are: age at first visit, disease group, MELD score (both as a continuous variable and a factor variable), and urgency of transplant. Three approaches (as outlined in Table 4.3, Section 4.3.1) were considered. The models were developed using SPSS. The forward stepwise regression procedure, with entry value set to 0.05 and removal value set to 0.10, was adopted. This appendix details the development of the three models.

The final section compares the distributions of age and primary liver disease for the patients from BLU who joined the national waiting list, with the observed distributions of patients on the whole of the UK Transplant (UKT) waiting list. This analysis confirms whether the models developed using BLU data could be generalised for use nationally.

I.2 Model Development and Goodness-of-Fit Tests

The three statistics: Hosmer and Lemeshow Test, Percentage of Correct Classifications, and Cox and Snell R^2 were used to develop the models and assess their goodness-of-fit.

Hosmer and Lemeshow Test

At each step, the Hosmer and Lemeshow Test provides a measure of the goodness-of-fit of the model, against the null hypothesis that the model

adequately fits the data. If the null hypothesis is true then that statistic should have an approximately chi-squared distribution with the displayed degrees of freedom. If the significance of the test is small (i.e., less than 0.05) then the model does not adequately fit the data.

Percentage of Correct Classifications

Assesses the performance of the model created by calculating the percentage of patient outcomes correctly classified by the model.

Cox and Snell R^2

The Cox and Snell R^2 statistic approximates the percentage of variation in the response that is explained by the model. A larger value indicates that more of the variation is explained by the model, to a maximum value of 1.

I.3 Model Development

This section summaries the results from the development of the three models and the covariates present in the final models.

I.3.1 Approach A

All patients considered in the logistic regression model. MELD score excluded from the analysis.

Table I.1 Referral Outcome Model Development Summary for Approach A.

Step	Hosmer and Lemeshow Test			Overall % Correct Classifications	Cox and Snell R^2
	χ^2	Degrees of freedom	Significance		
1	<0.001	0	.	66.4	0.052
2	<0.001	1	1.000	66.4	0.093
3	<0.001	2	1.000	67.4	0.107
4	<0.001	3	1.000	67.9	0.123
5	7.474	8	0.482	68.9	0.130
6	4.395	8	0.820	69.0	0.136

Table I.2 Resultant Referral Outcome Model for Approach A.

Attributes	B	Standard Error	Significance	Exp(B)
Age at First Visit	-0.021	0.008	0.007	0.979
Super Urgent of Acute Disease Group	1.748	0.614	0.004	5.743
Unknown Liver Disease	-1.506	0.325	<0.001	0.222
Cryptogenic Liver Disease	-1.113	0.289	<0.001	0.329
Alcoholic Liver Disease	-1.435	0.213	<0.001	0.238
Hepatitis C	-0.556	0.239	0.020	0.573
Constant	2.153	0.450	<0.001	8.608

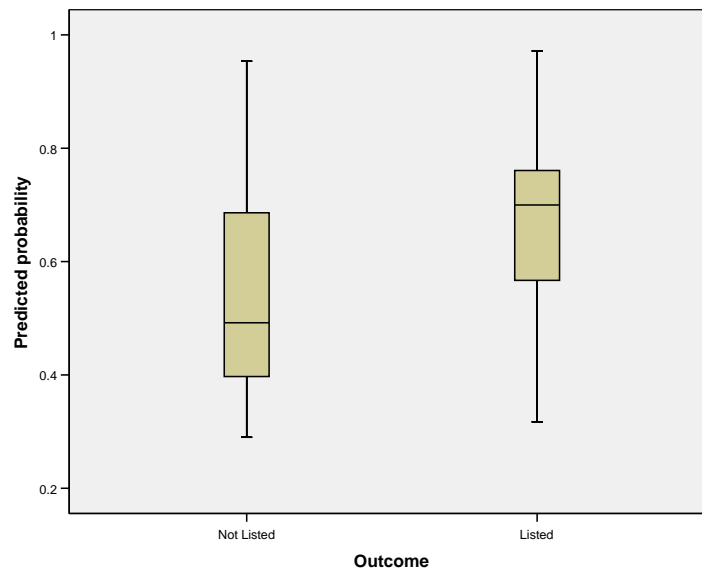


Figure I.1 Box Plot of the Predicted Probabilities as Estimated using the Final Model from Approach A, by the Observed Outcomes of Not Listed or Listed.

I.3.2 Approach B

Chronic Liver Disease patients only considered in the logistic regression model and the covariates age at first visit to the liver unit, disease group, patient gender, and MELD score as a continuous covariate.

Table I.3 Referral Outcome Model Development Summary for Approach B.

Step	Hosmer and Lemeshow Test			Overall % Correct Classifications	Cox and Snell R ²
	χ^2	Degrees of freedom	Significance		
1	<0.001	0	.	63.8	0.044
2	<0.001	1	1.000	64.9	0.060
3	<0.001	2	1.000	65.3	0.077
4	4.482	8	0.811	66.2	0.084
5	3.766	8	0.878	66.2	0.092
6	2.124	8	0.977	66.2	0.099

Table I.4 Resultant Referral Outcome Model for Approach B.

Attributes	B	Standard Error	Significance	Exp(B)
Age at First Visit	-0.022	0.008	0.007	0.978
Unknown Liver Disease	-1.503	0.328	<0.001	0.222
Cryptogenic Liver Disease	-1.068	0.292	<0.001	0.344
Alcoholic Liver Disease	-1.457	0.214	<0.001	0.233
Hepatitis C	-0.594	0.241	0.014	0.552
MELD score (continuous)	-0.026	0.011	0.021	0.974
Constant	2.641	0.513	<0.001	14.021

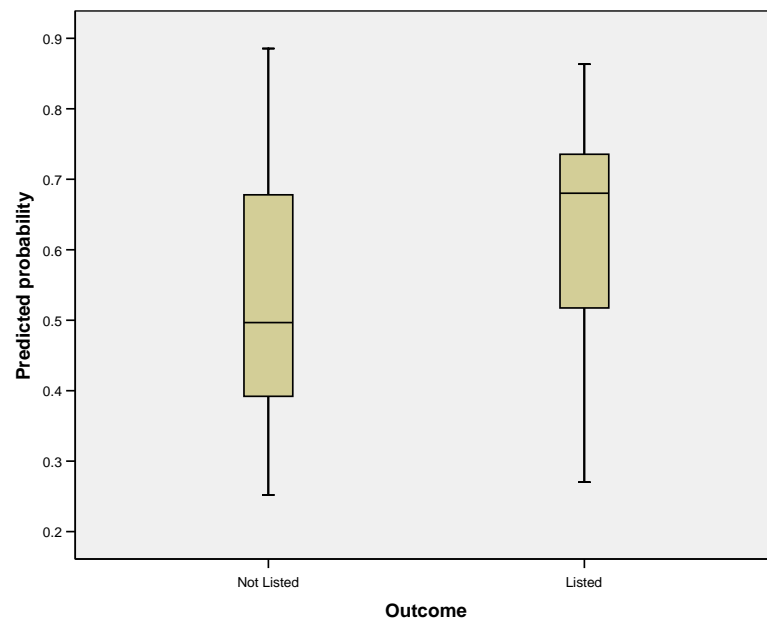


Figure I.2 Box Plot of the Predicted Probabilities as Estimated using the Final Model from Approach B, by the Observed Outcomes of Not Listed or Listed.

I.3.3 Approach C

Chronic Liver Disease patients only considered in the logistic regression model and the covariates age at first visit to the liver unit, disease group, patient gender, and MELD score as 4 factor covariates.

Table I.5 Referral Outcome Model Development Summary for Approach C.

Step	Hosmer and Lemeshow Test			Overall % Correct Classifications	Cox and Snell R ²
	χ^2	Degrees of freedom	Significance		
1	<0.001	0	.	63.8	0.044
2	0.320	2	0.852	63.8	0.073
3	0.382	4	0.984	64.7	0.085
4	1.526	4	0.822	65.3	0.099
5	4.901	8	0.768	67.4	0.109
6	4.946	8	0.763	66.2	0.118

Table I.6 Resultant Referral Outcome Model for Approach C.

Attributes	B	Standard Error	Significance	Exp(B)
Age at First Visit	-0.025	0.008	0.003	0.975
Unknown Liver Disease	-1.391	0.330	<0.001	0.249
Cryptogenic Liver Disease	-1.072	0.296	<0.001	0.342
Alcoholic Liver Disease	-1.510	0.218	<0.001	0.221
Hepatitis C	-0.645	0.244	0.008	0.525
MELD Group 2	0.765	0.173	<0.001	2.149
Constant	1.938	0.462	<0.001	6.948

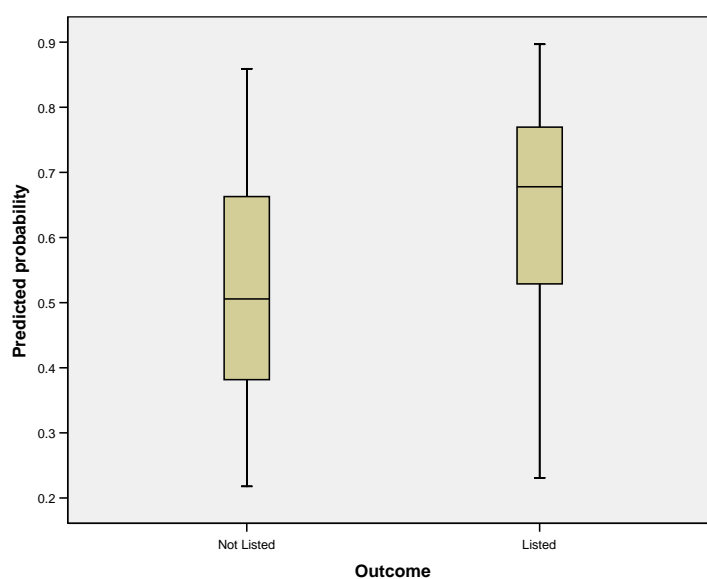


Figure I.3 Box Plot of the Predicted Probabilities as Estimated using the Final Model from Approach C, by the Observed Outcomes of Not Listed or Listed.

I.4 Comparing BLU and UKT Patient Mixes

I.4.1 Comparing Disease Group Distributions

Table I.7 Frequencies by Patient Disease Groups observed to join the Waiting List in Both the UKT and BLU data sets.

Disease Group	UKT	BLU
Other Cirrhotic Diseases	428	170
Cholestatic Liver Disease	197	56
Cancer	56	2
Metabolic Liver Disease	71	34
Other Diagnosed Liver Disease	155	4
Super Urgent/Acute Liver Disease	523	65
Unknown and Not Reported Liver Diseases	82	53
Hepatitis B	84	22
Cryptogenic Liver Disease	154	62
Alcoholic Liver Disease	404	154
Hepatitis C	299	114
Grand Total	2453	736
	χ^2 p-value	1.124x10-263

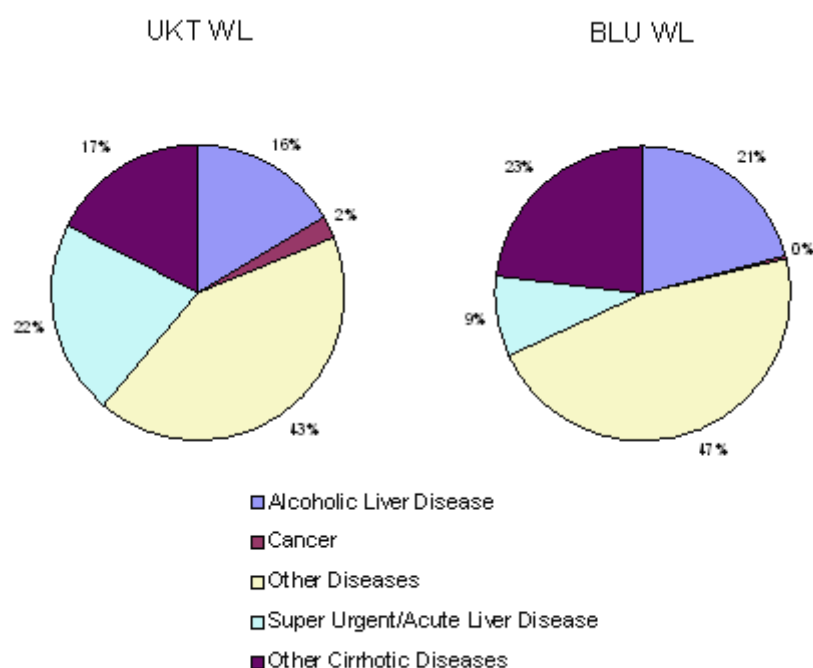


Figure I.4 Differences in Indications for Listing within the UKT and BLU cohorts.

Table I.7 and Figure I.4 indicate that there are significant differences between the indications (diseases) for which patients are listed on the waiting list, at BLU compared to the national proportions.

I.4.2 Comparing Age Group Distributions

Table I.8 Frequencies by Patient Age Groups observed to join the Waiting List in Both the UKT and BLU data sets.

Patient Age Group	UKT	BLU
17-20	86	13
21-25	84	15
26-30	94	17
31-35	165	41
36-40	199	53
41-45	256	71
46-50	322	128
51-55	421	127
56-60	396	121
61-65	290	99
66 plus	140	51
Grand Total	2453	736
	χ^2 p-value	5.3842x10-254

Table I.8 indicates that there are significant differences between the age groups of patients listed on the waiting list, by BLU compared to the national proportions.

Appendix J

Waiting List Outcome Model Analysis and Development

This appendix reports the development of the two models:

- (1) A survival model which captures the event death/removal (DR) censored at all other events from the waiting list (WL); and
- (2) A competing risks model which captures the two events (1) death/removal, and (2) Transplantation, censored at all other events from the waiting list.

J.1 Preliminary Analysis

This section summarises the main findings of the preliminary analysis (as outlined in Section 3.6.3 part [A]). Only the graphs and tests which help to decide which parametric models are appropriate are presented here, however the analysis was performed for all covariates.

J.1.1 Identifying Significant Differences in Patient Survival by Covariate Levels

Table J.1 gives a summary of the Log Rank and Wilcoxon tests (pooled over strata) which were used to identify the covariates by which the survival curves were significantly different. The tests were based on identifying the outcome death/removal and censoring at all other outcomes.

Table J.1 Tests to Identify Covariates which Lead to Significantly Different Survival Outcomes from the WL.

Significance of Tests	Log Rank	Wilcoxon (Breslow)	Tarone-Ware
First Transplant	<0.001	<0.001	<0.001
Disease Group	<0.001	<0.001	<0.001
Gender	0.964	0.369	0.499
Urgency	<0.001	<0.001	<0.001
Blood Group	0.841	0.929	0.957
Weight Group	0.391	0.121	0.167
Age Group	0.013	<0.001	<0.001
Transplant Centre	0.012	0.009	0.010

Survival functions are significantly different over the following factors: first transplant or not, disease group, transplant urgency status, age group, and the transplant centre at which the patient is registered. Pair-wise comparisons for levels within each covariate also gave similar conclusions but identified which levels were most different.

J.1.2 Should there be two separate models for different Transplant Urgency Statuses?

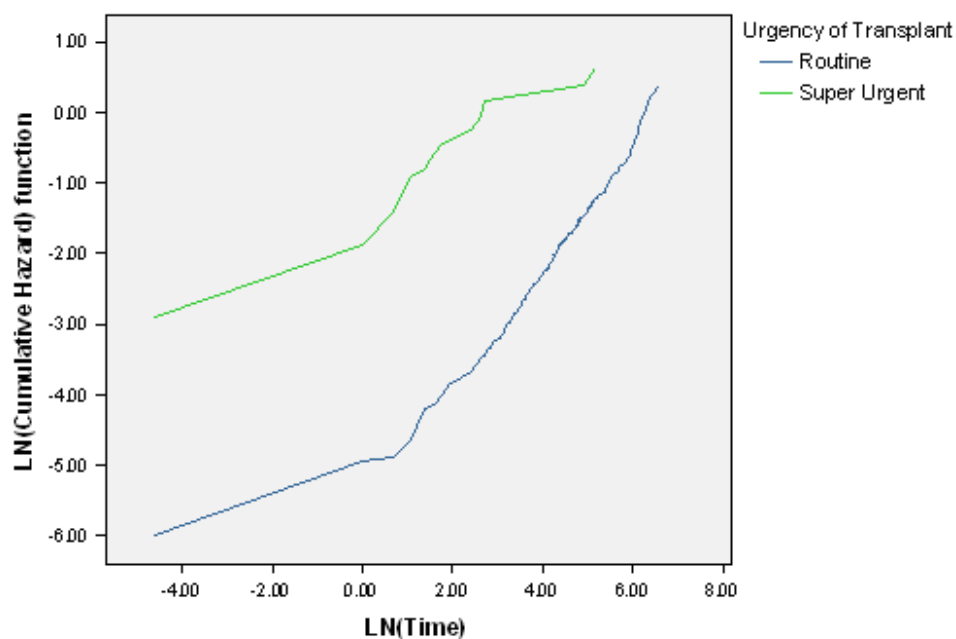


Figure J.1 Log-Cumulative Hazard Plot, by transplant urgency.

Figure J.1 tests whether the Proportional Hazards (PH) assumption holds in modelling the survival distributions by transplant urgency status. It shows a reasonably straight line for the patients requiring transplants as routine urgency, however, the vertical distance between the two lines is not constant through log time, and so two models may be required. Further plots indicated that the PH could be assumed for the routine patients.

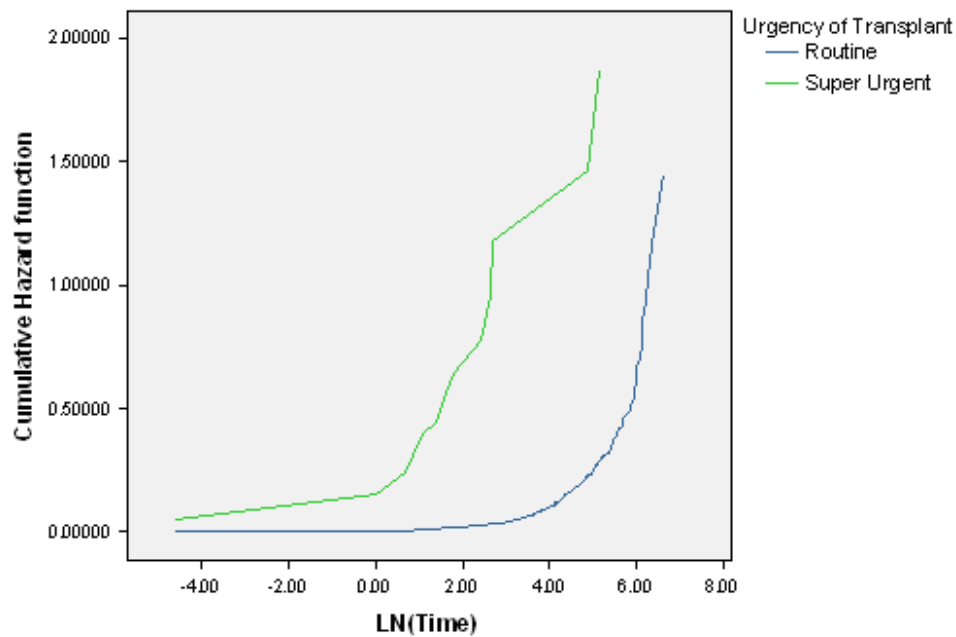


Figure J.2 Cumulative Hazard Plot, by transplant urgency.

Figure J.2 considers whether the Accelerated Failure Time (AFT) assumption holds in modelling the survival distributions by transplant urgency status. It shows a reasonable straight line for the patients requiring super urgent transplants, however, the line representing observations for those requiring a routine transplant is not straight. This means that a AFT is not appropriate for modelling survival if considering all the patients, however, it may be applied if just the survival times for the patients requiring a super urgent transplant are being modelled (more Cumulative Hazard Plots need to be analysed to confirm this).

J.1.3 Is a PH survival model appropriate?

The log-cumulative hazard plots for routine patients split by the covariates: primary disease group, transplant unit, and age group, resulted in reasonably straight parallel lines (not shown here) which would confirm that the PH assumption is satisfied across these covariates.

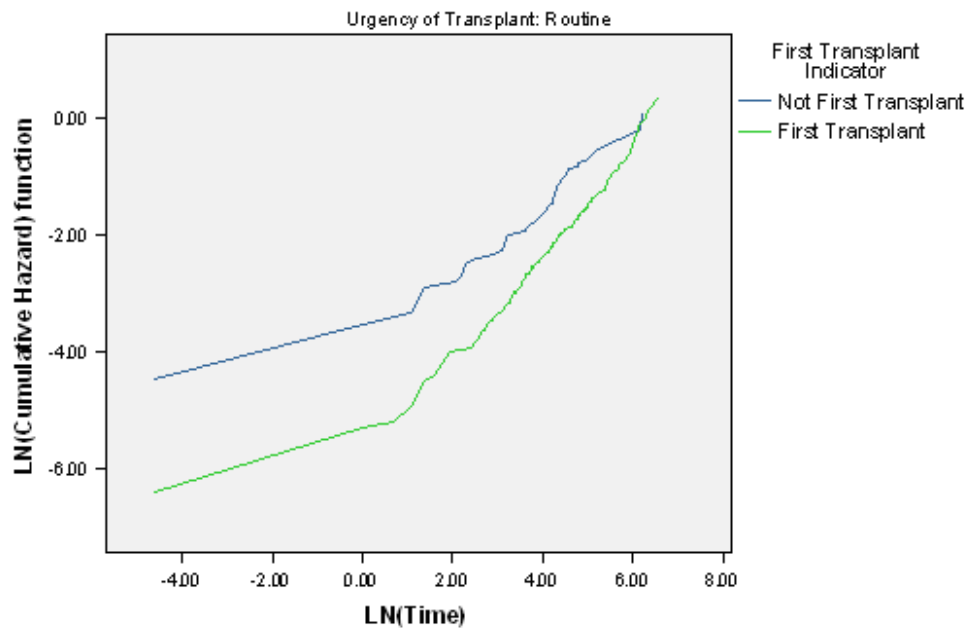


Figure J.3 Log-Cumulative Hazard Plot, by first transplant indicator for Routine patients.

Figure J.3 presents the log-cumulative hazard plot by first transplant or not. It can be seen that although these lines are reasonably straight, they are not parallel (and therefore cross). This suggests that a stratified model may be more applicable in capturing the survival of the routine patients.

J.1.4 Is an AFT survival model appropriate?

The cumulative hazard plots for super urgent patients by the covariates first transplant indicator, transplant unit, and age group, returned reasonably straight parallel lines to suggest that AFT models would be appropriate in capturing the survival of super urgent patients. The lines on these graphs were fairly close

together, which suggests that the survival of patients within the different groups may not be significantly different.

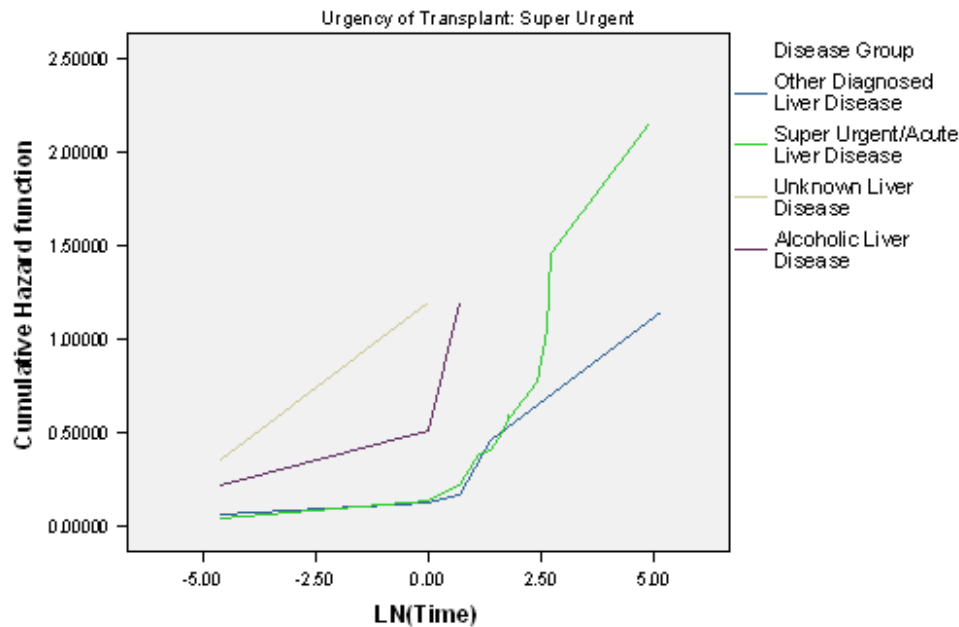


Figure J.4 Cumulative Hazard Function Plot, by disease group for Super Urgent patients.



Figure J.5 Cumulative Hazard Plot, by patient gender for Super Urgent patients.

Figures J.4 and J.5 show the plots by disease group and patient gender, respectively. The split by disease group suggests differences in survival between the groups, however, some lines are constructed of very few data points. The split by gender also seem to provide reasonably straight lines, but the lines are further apart which may suggest significant differences between male and female survival chances.

Is a Log-Logistic AFT survival model appropriate?

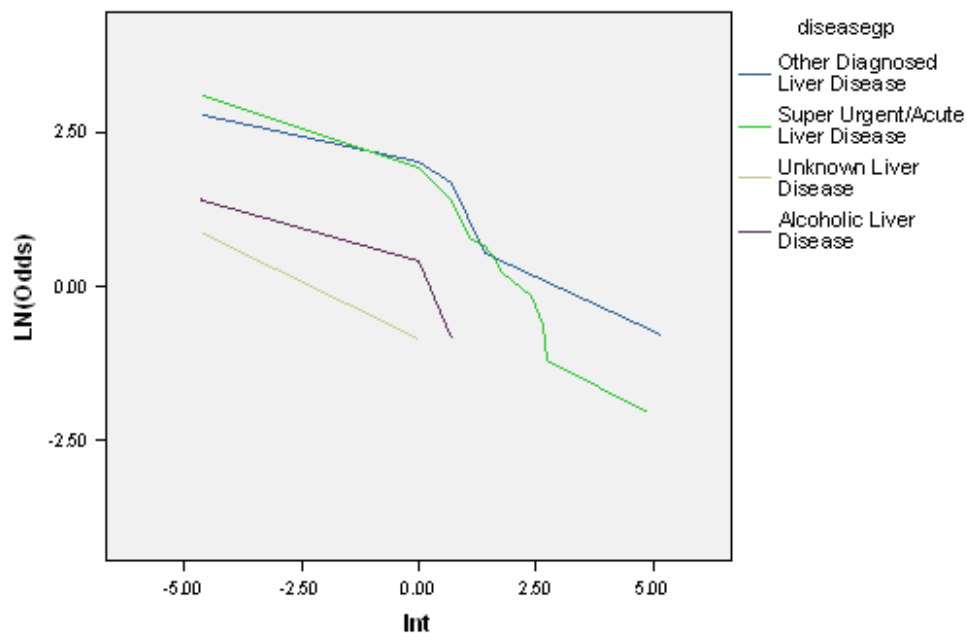


Figure J.6 The Log-Odds Plot for Super Urgent patients by disease group.

Figure J.6 shows that the log-odds plots by disease group are reasonably straight and parallel, suggesting that a log-logistic survival model could be used in capturing the survival times.

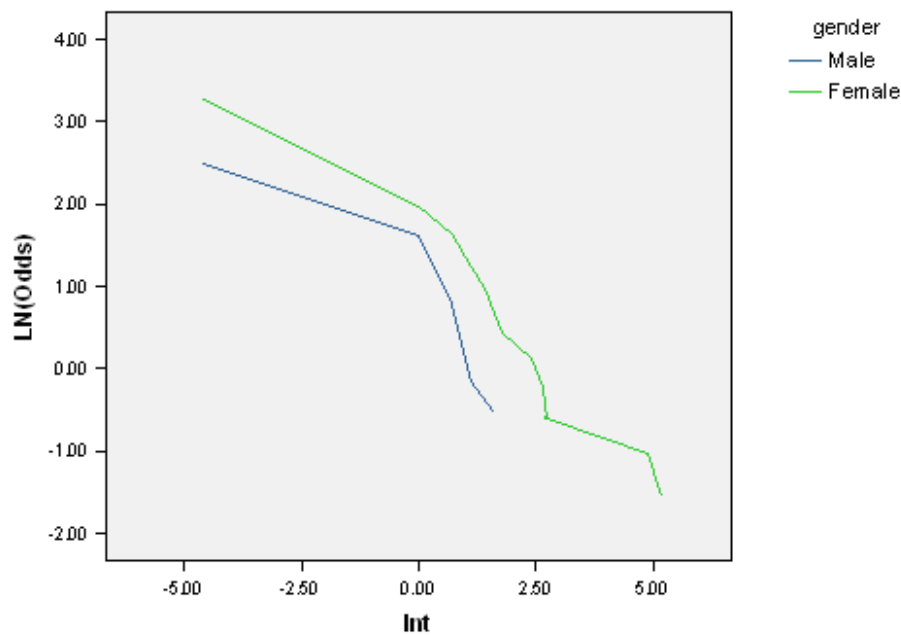


Figure J.7 The Log-Odds Plot for Super Urgent patients by patient gender.

Figure J.7 shows that the log-odds plots by transplant urgency are reasonably straight and parallel, suggesting that a log-logistic survival model could be used in capturing the survival times.

Is a Lognormal AFT survival model appropriate?

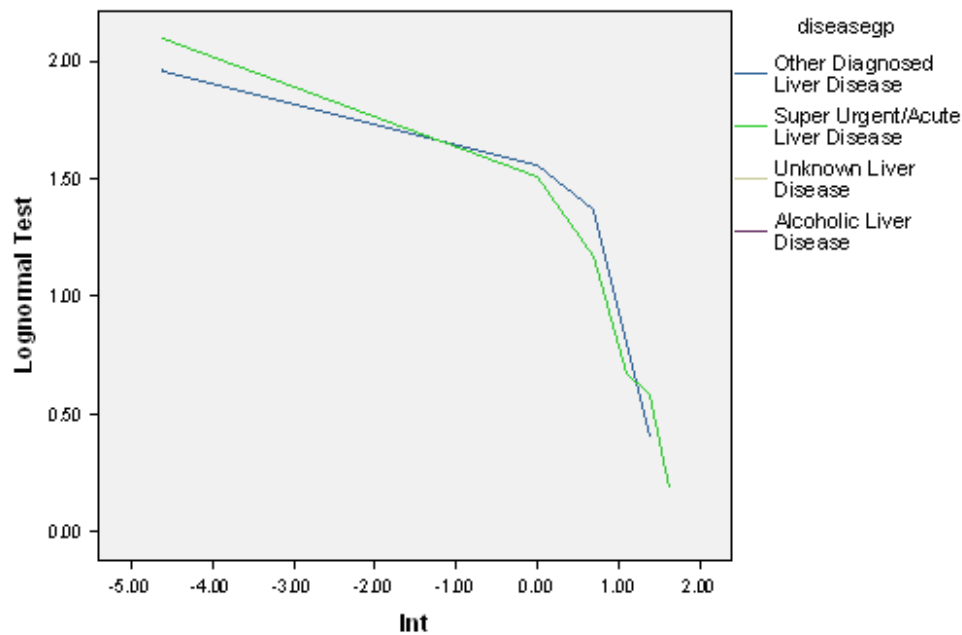


Figure J.8 Testing the overall lognormal AFT assumption for Super Urgent patients, plot by disease group.

Figure J.8 shows that the curves by transplant urgency are reasonably straight and parallel, suggesting that a log-logistic survival model could be used in capturing the survival times.

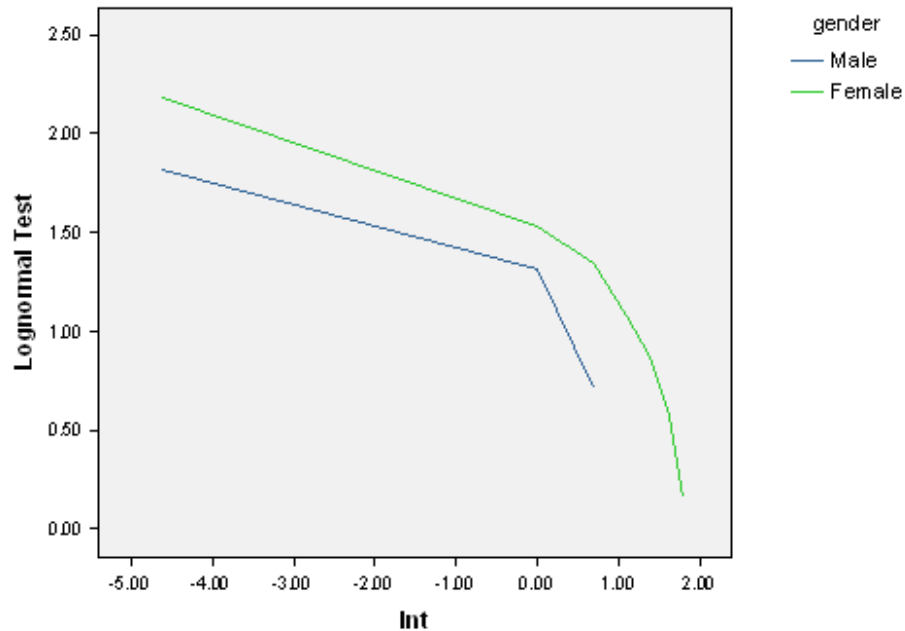


Figure J.9 Testing the overall lognormal AFT assumption for Super Urgent patients, plot by patient gender.

Figure J.9 shows that the curves by patient gender are reasonably straight and parallel, suggesting that a log-logistic survival model could be used in capturing the survival times.

To summarise, Figures J.6-J.9 show that either the log-logistic or the lognormal survival models are appropriate for the modelling of the death/removal times for the patients requiring a super urgent transplant, and show that a log-logistic model may be more applicable in modelling the outcome.

J.1.5 Is a PH competing risks model appropriate?

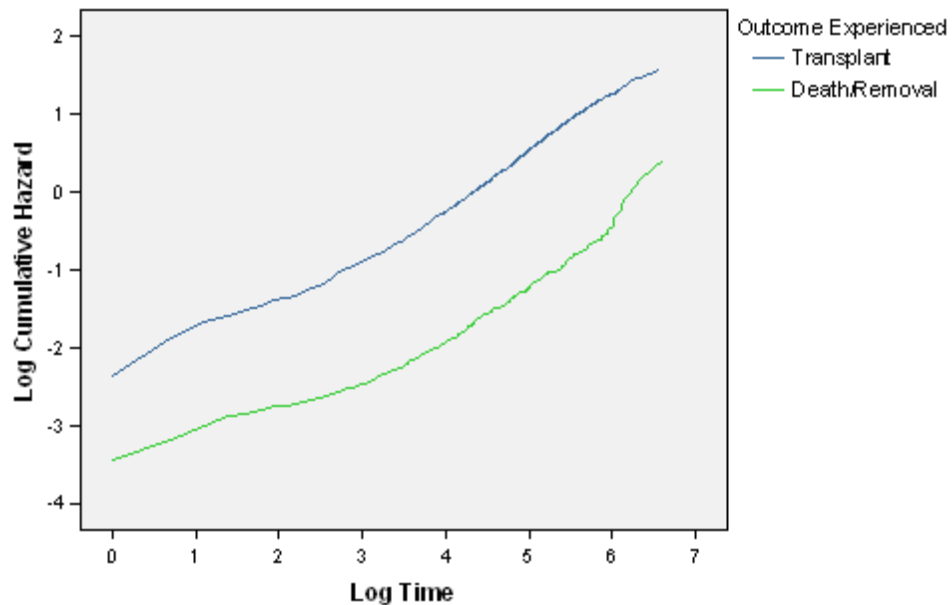


Figure J.10 Checking the Proportional Hazards Assumption of the Competing Risks Model for Outcomes from the Waiting List.

Figure J.10 suggests that a PH competing risk model would not be suitable in capturing the outcomes to transplantation and death/removal, from the waiting list.

J.1.6 Is an AFT competing risks model appropriate?

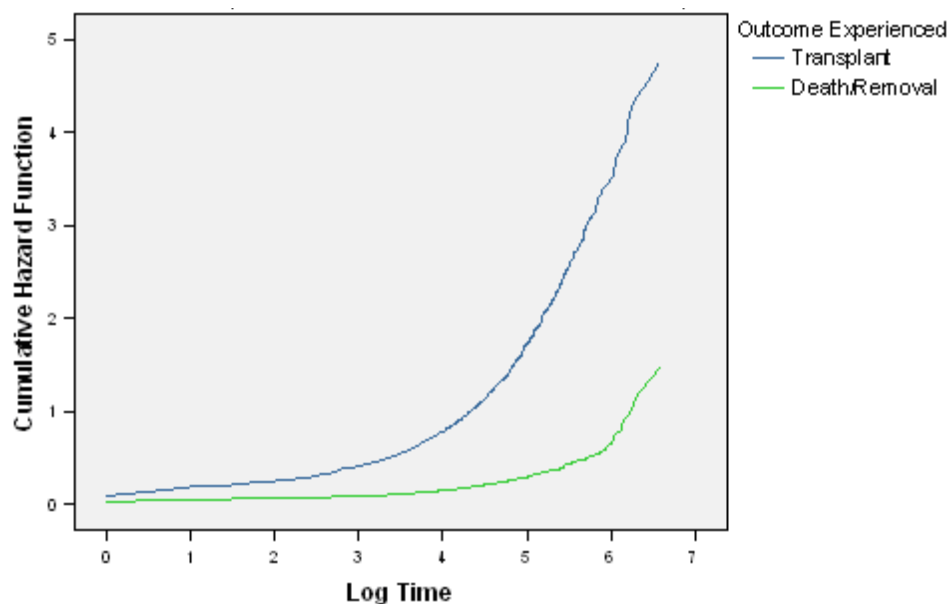


Figure J.11 Checking the Accelerated Failure Time Assumption of the Competing Risks Model for Outcomes from the Waiting List.

The cumulative hazard plot in Figure J.11 suggests that an AFT competing risk model would be suitable in capturing the outcomes to transplantation and death/removal, from the waiting list.

J.1.7 Summary

The attributes which significantly influence death/removal outcome from the waiting list, are: first transplant or not, disease group, transplant urgency status, age group, and transplant centre.

The models which would adequately capture the outcomes from the waiting list, are:

- (1) Two survival models (for the curves depicted in Figure J.12). The first assuming the AFT assumption for generating survival times for patients requiring super urgent transplants and the second a Weibull model which assumes the PH assumption, stratified by first transplant or not; or
- (2) A Weibull (AFT) competing risks model which considered the outcomes death/removal and transplanted, censored at all other events.

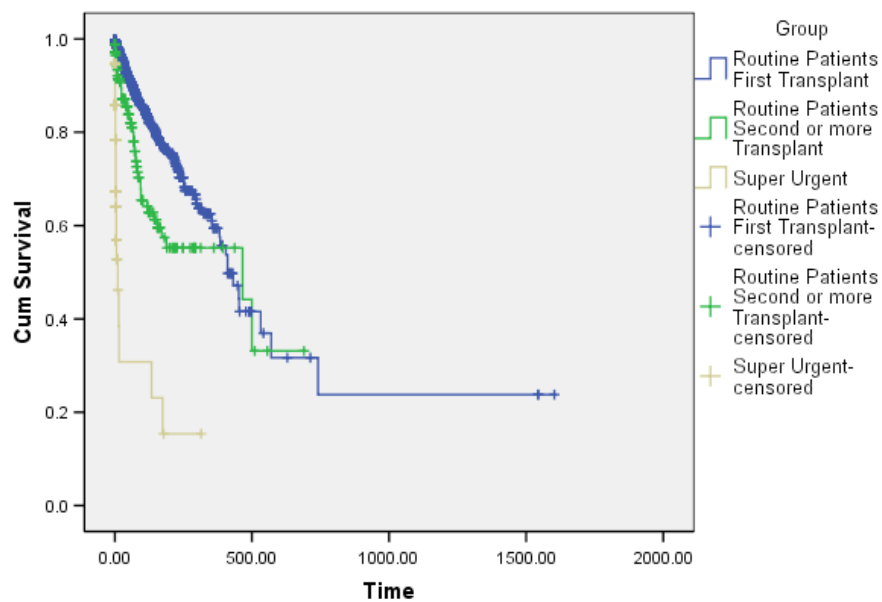


Figure J.12 Overall Kaplan-Meier estimates for survival by the patient groups 1) those requiring a super urgent transplant, 2) those requiring their first routine transplant, and 3) those requiring subsequent routine transplants.

Figure J.12 shows that the survival times (DR times from the waiting list) are initially worse for routine patients waiting for their second or more transplant, when compared to routine patients waiting for their first transplant. However, after two years the survival rates are similar for both groups.

J.2 Parametric Model Development & Goodness of Fit

This section summarises the parametric models developed using the process as outlined in Section 3.6.3 part [B].

J.2.1 Log-logistic Survival model for SU patients

J.2.1.1 Model Development - Log-logistic Survival model for SU patients

Table J.2 The overall development process for the Log-logistic model which considers all Super Urgent patients.

Stage	Enter/Exit	Variable(s)	Loglik(model)
a)	Enter	-Super Urgent or Acute Disease Group -Unknown Liver Disease Group -Alcoholic Liver Disease -Gender -Age at Registration -First Transplant or not	-318.9
b)	Exit	-First Transplant or not	-318.9
	Exit	-Super Urgent or Acute Disease Group	-319.1
	Exit	-Age at Registration	-319.8
c)	-	-Unknown Liver Disease Group -Alcoholic Liver Disease -Gender	-319.8

J.2.1.2 Final Model - Log-logistic Survival model for SU patients

Table J.3 Log logistic Survival model for SU patients.

Attributes	Coefficient	Standard error	Z	p-value
(Intercept)	2.914	0.2842	10.25	1.14x10-024
Unknown Liver Disease Group	-3.024	0.8476	-3.57	3.59x10-004
Alcoholic Liver Disease	-1.892	1.1387	-1.66	9.65x10-002
Gender	-0.749	0.3241	-2.31	2.09x10-002
Standard deviation	1.38			
Log(std dev)	0.320	0.0859	3.72	1.98x10-004

Loglik(model)= -319.8 Loglik(intercept only)= -331.7

Chisq= 23.74 on 3 degrees of freedom, p= 0.000028

J.2.1.3 Goodness of Fit - Log-logistic Survival model for SU patients

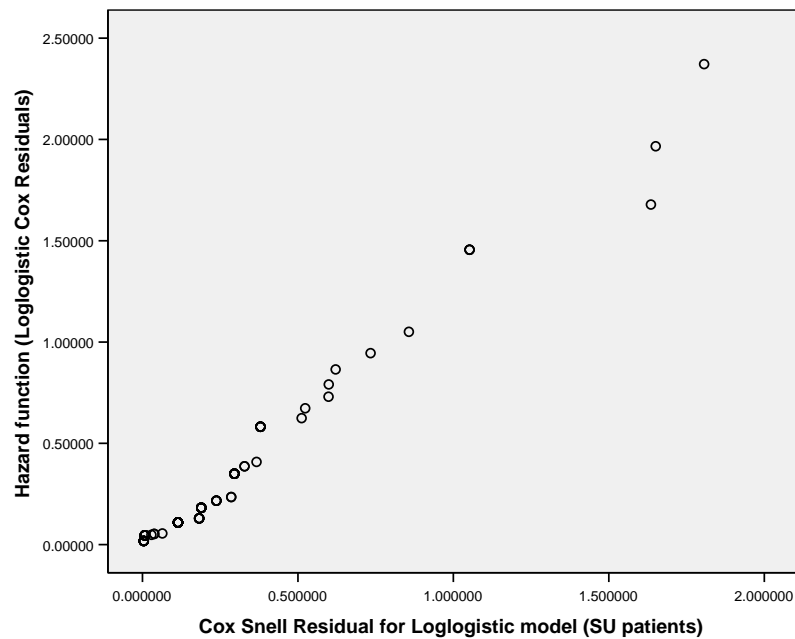


Figure J.13 Cumulative hazard plot of the Cox-Snell residuals generated from the Log-logistic model developed for the super urgent patients.

Table J.4 The result (model summary and coefficients) of performing linear regression (with no covariates) on the graph depicted in Figure J.13.

Model	Unstandardised Coefficients		Standardised Coefficients	t	Significance
	B	Std. Error	Beta		
(Constant)	-0.015	0.009		-1.785	0.077
Cox Snell Residual for Loglogistic model (SU patients)	1.255	0.021	0.986	61.092	<0.001

$R^2 = 0.972$

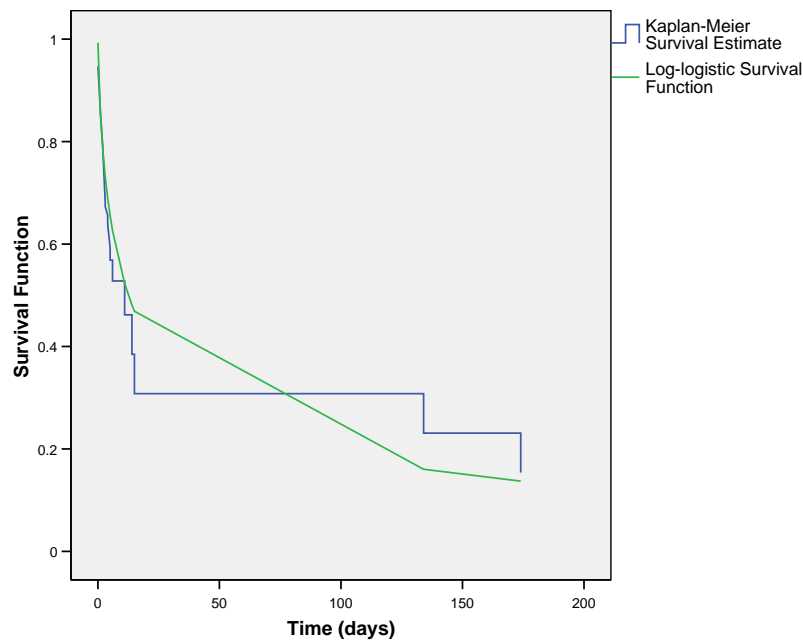


Figure J.14 Plot of the Kaplan-Meier estimate for survival and the estimated log-logistic model, for the super urgent patients.

Figure J.14 graphs the Kaplan-Meier Estimate (for the death/removal outcome) derived from the data and the final log-logistic curve, for the patients waiting for a super urgent transplant. It can be seen the log-logistic model provides a reasonable estimate of the times observed in the data.

J.2.2 Weibull Survival model for Routine patients going for First Transplant

J.2.2.1 Model Development - Weibull Survival model for Routine patients going for First Transplant

Table J.5 The overall development process for the Weibull model which considers all Routine patients going for their First Liver Transplant.

Stage	Enter/Exit	Variable(s)	Loglik(model)
a)	Enter	-Other Cirrhotic Disease Group -Unknown Liver Disease Group -Cryptogenic Liver Disease -Age at Registration -Centre A -Centre B -Centre D	-1732.7
b)	Exit	-Cryptogenic Liver Disease	-1733.2
	Exit	-Centre B	-1734.3
	Exit	-Centre A	-1735.5
c)	-	-Other Cirrhotic Disease Group -Unknown Liver Disease Group -Age at Registration -Centre D	-1735.5

J.2.2.2 Final Model - Weibull Survival model for Routine patients going for First Transplant

Table J.6 Final Model for Capturing the DR time from joining the WL for patients waiting for their first routine transplant (Weibull model).

Attributes	Coefficient	Standard error	Z	p-value
(Intercept)	7.4888	0.37107	20.18	1.43x10-090
Other Cirrhotic Disease Group	0.7071	0.20281	3.49	4.89x10-004
Unknown Liver Disease Group	-0.6994	0.27466	-2.55	1.09x10-002
Age at Registration	-0.0198	0.00668	-2.97	2.97x10-003
Centre D	0.6409	0.29592	2.17	3.03x10-002
Standard deviation	1.1			
Log(std dev)	0.0972	0.04874	1.99	4.62x10-002

Loglik(model)= -1735.5 Loglik(intercept only)= -1752.3

Chisq= 33.47 on 4 degrees of freedom, p= 9.6x10-007

J.2.2.3 Goodness of Fit - Weibull Survival model for Routine patients going for First Transplant

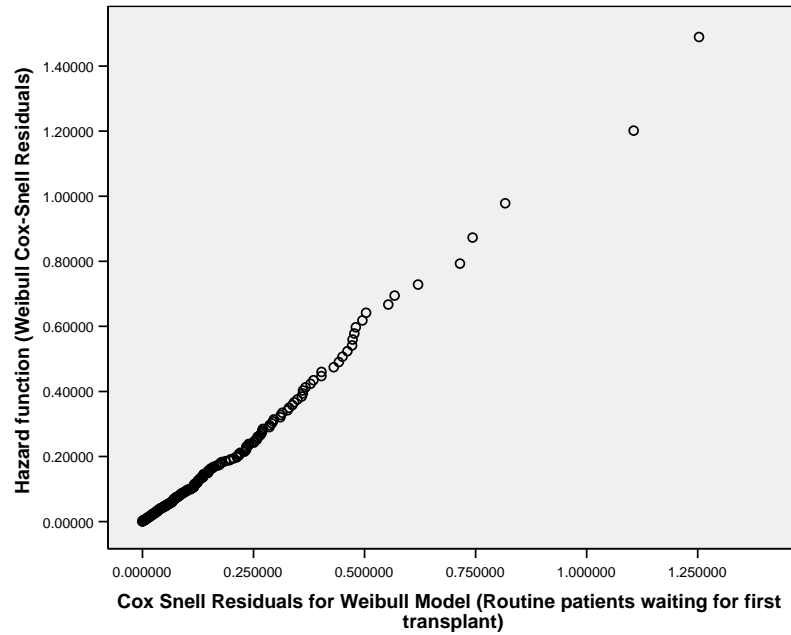


Figure J.15 Cumulative hazard plot of the Cox-Snell residuals generated from the Weibull model developed for the routine patients going for their first liver transplant.

Table J.7 The result (model summary and coefficients) of performing linear regression (with no covariates) on the graph depicted in figure J.15

Model	Unstandardised Coefficients		Standardised Coefficients	t	Significance
	B	Std. Error	Beta		
(Constant)	-0.015	0.001		-10.163	<0.001
Cox Snell Residual for Weibull model (Routine 1 st Transplants)	1.155	0.006	0.997	184.157	<0.001

$R^2 = 0.993$

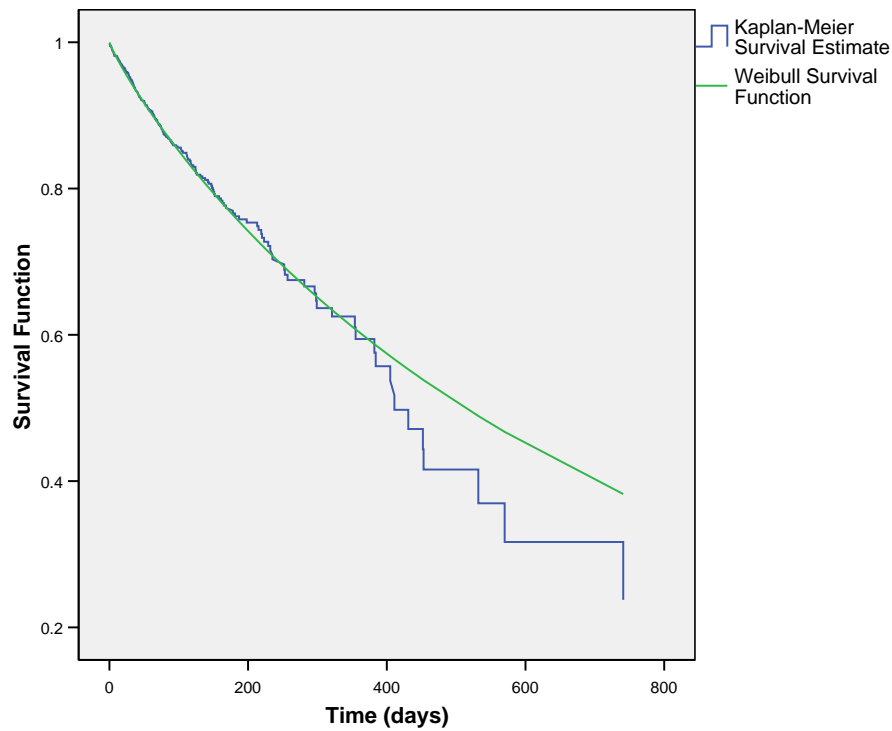


Figure J.16 Plot of the Kaplan-Meier estimate for survival and the estimated Weibull model, for the routine patients going for their first liver transplant.

Figure J.16 graphs the Kaplan-Meier Estimate (for the death/removal outcome) derived from the data and the final Weibull curve for routine patients waiting for their first transplant. It can be seen the Weibull model provides a reasonable estimate of the times observed in the data.

J.2.3 Weibull Survival model for Routine patients going for Successive Transplant

J.2.3.1 Model Development - Weibull Survival model for Routine patients going for Successive Transplant

Table J.8 The overall development process for the Weibull model which considers all Routine patients going for their second or more Liver Transplant.

Stage	Enter/Exit	Variable(s)	Loglik(model)
a)	Enter	-Metabolic Liver Disease -Unknown Liver Disease Group -Centre B -Centre D	-318.6
b)	Exit	-Metabolic Liver Disease	-318.9
c)	-	-Unknown Liver Disease Group -Centre B -Centre D	-318.9
	Enter	-Unknown Liver Disease Group -Centre B -Centre D -Centre C	-317.3

J.2.3.2 Final Model - Weibull Survival model for Routine patients going for Successive Transplant

Table J.9 Final Model for Capturing the DR time from joining the WL for patients waiting for their second or greater routine transplant (Weibull model).

Attributes	Coefficient	Standard error	Z	p-value
(Intercept)	6.518	0.340	19.20	3.98x10-082
Unknown Liver Disease Group	-2.543	0.940	-2.71	6.83x10-003
Centre B	-1.281	0.619	-2.07	3.85x10-002
Centre C	1.456	0.909	1.60	1.09x10-001
Centre D	-2.210	0.839	-2.64	8.40x10-003
Standard deviation	1.54			
Log(std dev)	0.432	0.119	3.62	2.95x10-004

Loglik(model)= -317.3 Loglik(intercept only)= -324.9

Chisq= 15.28 on 4 degrees of freedom, p= 0.0041

J.2.3.3 Goodness of Fit - Weibull Survival model for Routine patients going for Successive Transplant

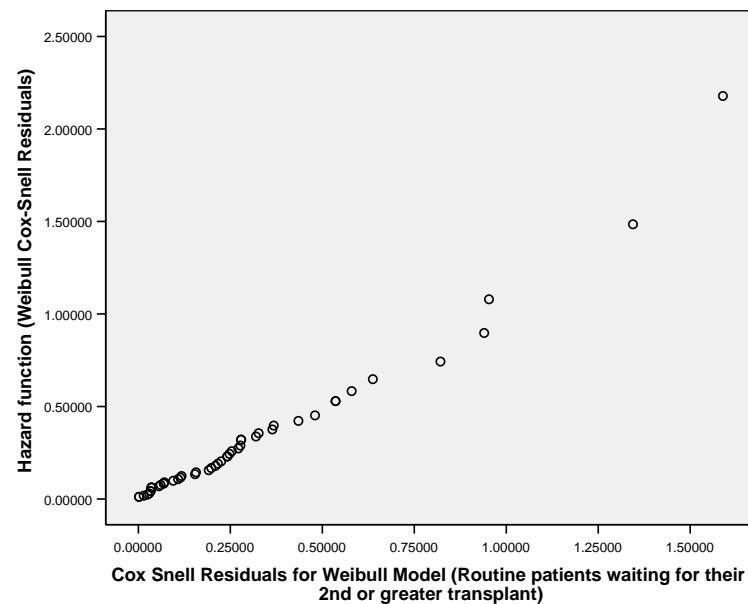


Figure J.17 Cumulative hazard plot of the Cox-Snell residuals generated from the Weibull model developed for the routine patients going for their second or more liver transplant.

Table J.10 The result (model summary and coefficients) of performing linear regression (with no covariates) on the graph depicted in Figure J.17.

Model	Unstandardised Coefficients		Standardised Coefficients	t	Significance
	B	Std. Error	Beta		
(Constant)	-0.031	0.014		-2.184	0.034
Cox Snell Residual for Weibull model (Routine successive Transplants)	1.162	0.031	0.984	37.005	<0.001

$R^2 = 0.967$

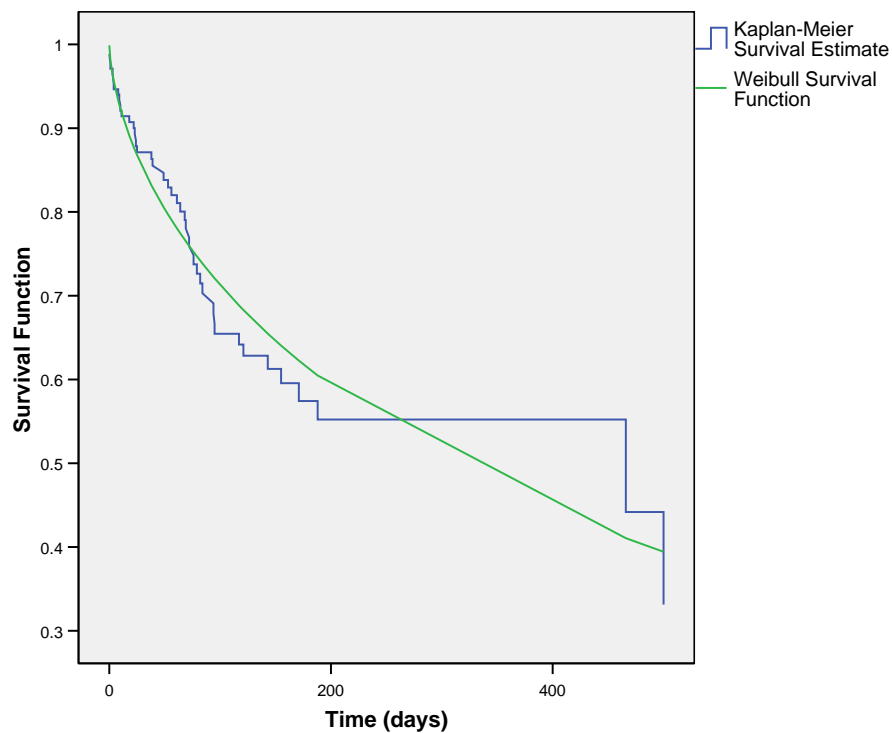


Figure J.18 Plot of the Kaplan-Meier estimate for survival and the estimated weibull model, for the routine patients going for their second or more liver transplant.

Figure J.18 graphs the Kaplan-Meier Estimate (for the death/removal outcome) derived from the data and the final Weibull curve for routine patients waiting for their successive transplant. It can be seen the Weibull model provides a reasonable estimate of the times observed in the data.

J.2.4 Weibull Competing Risks Model

J.2.4.1 Final Model - Weibull Competing Risks Model

Table J.11 Final Model for Capturing the DR time and time to Transplant from joining the WL (Weibull Competing Risks model).

Attributes	Coefficient t/Value	Standard error	Z	p-value
(Intercept)	5.06133	0.12985	38.9786	<0.001
Cancer	-0.44636	0.16072	-2.7772	5.48x10-03
Other Diagnosed Disease	0.52442	0.10581	4.9561	7.19x10-07
Hepatitis B	-0.17709	0.13174	-1.3443	1.79x10-01
Centre B	-0.26666	0.06979	-3.8208	1.33x10-04
Centre E	0.09479	0.05988	1.5829	1.13x10-01
Gender	-0.35211	0.05961	-5.9067	3.49x10-09
Delta	2.50108	0.35208	7.1038	1.21x10-12
Age at Registration	-0.00624	0.00227	-2.7542	5.88x10-03
Other Cirrhotic Disease	-0.00596	0.07676	-0.0776	9.38x10-01
Disease Not Reported	0.65187	0.21251	3.0674	2.16x10-03
Centre C	-0.27779	0.08499	-3.2686	1.08x10-03
Transplant Urgency	-3.47336	0.08161	-42.5615	<0.001
Gender:Delta	0.18371	0.15962	1.1509	2.50x10-01
Age at Registration:Delta	-0.01142	0.00618	-1.8479	6.46x10-02
Strata(first transplant or not):Delta	0.25869	0.12553	2.0608	3.93x10-02
Other Cirrhotic Disease:Delta	0.63483	0.24698	2.5704	1.02x10-02
Disease Not Reported:Delta	-2.00983	0.3427	-5.8647	4.50x10-09
Centre C:Delta	0.57704	0.26424	2.1838	2.90x10-02
Transplant Urgency:Delta	-0.79344	0.19738	-4.0199	5.82x10-05
<i>etype=T, firsttx=1</i>	<i>0.138</i>	<i>0.0164</i>	<i>8.36</i>	<i>6.03x10-017</i>
Scale				
<i>etype=DR, firsttx=0</i>	<i>1.61</i>			
<i>etype=DR, firsttx=1</i>	<i>1.27</i>			
<i>etype=T, firsttx=0</i>	<i>1.39</i>			
<i>etype=T, firsttx=</i>	<i>1.15</i>			

Loglik(model)= -12599.4 Loglik(intercept only)= -13991.5

Chisq= 2784.05 on 19 degrees of freedom, p= 0

J.2.4.2 Goodness of Fit - Weibull Competing Risks Model

Figures J.19-J.22 show that the competing risks model captures the outcomes to death/removal and to transplantation from the waiting list very closely.

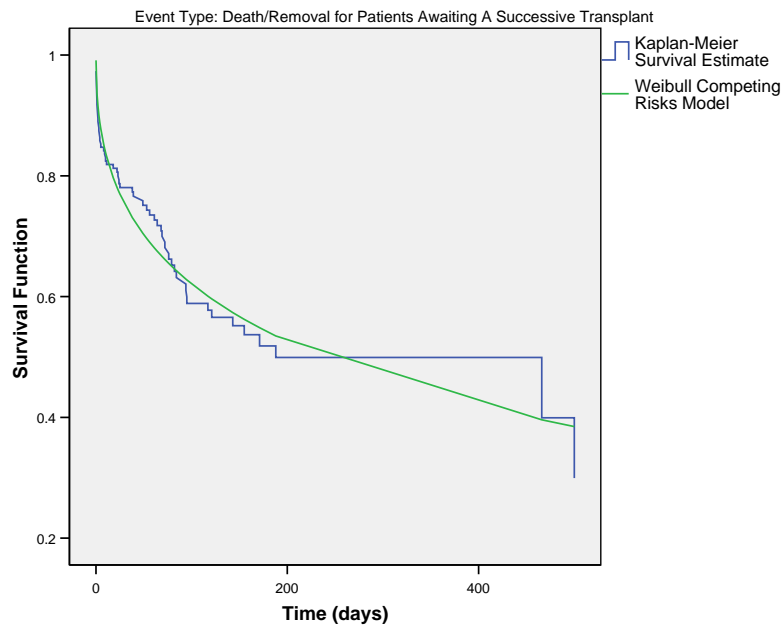


Figure J.19 Plot of the Kaplan-Meier estimate for survival and the estimated Weibull competing risks mode capturing the DR outcome from the WL, for patients awaiting a successive transplant.

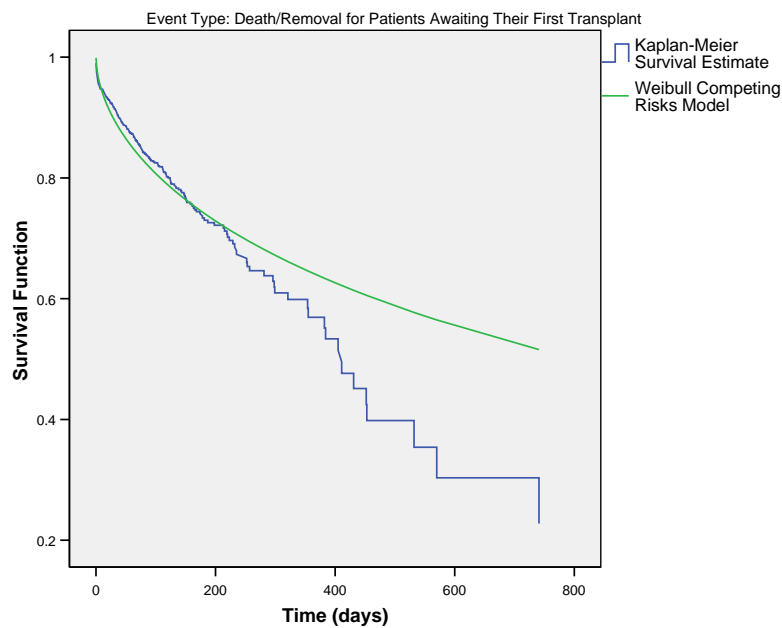


Figure J.20 Plot of the Kaplan-Meier estimate for survival and the estimated Weibull competing risks mode capturing the DR outcome from the WL, for patients awaiting their first transplant.

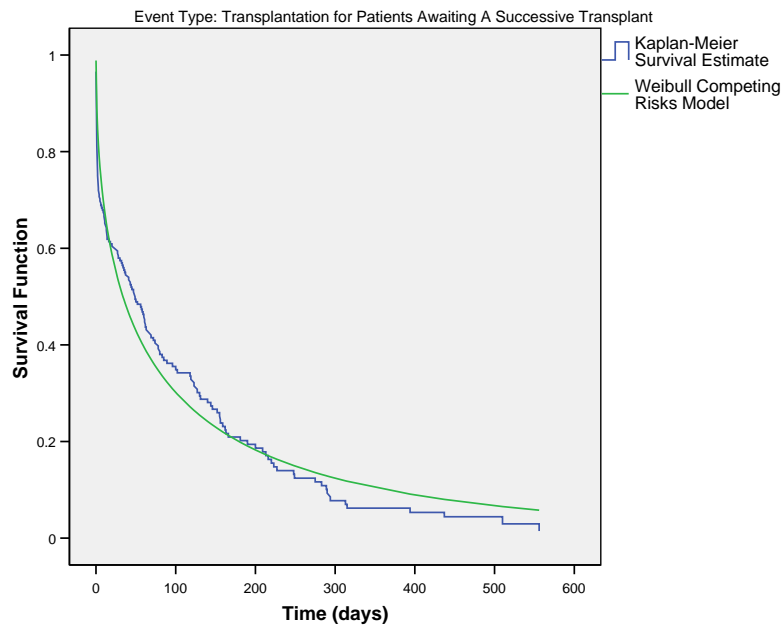


Figure J.21 Plot of the Kaplan-Meier estimate for survival and the estimated Weibull competing risks mode capturing the Transplantation outcome from the WL, for patients awaiting a successive transplant.

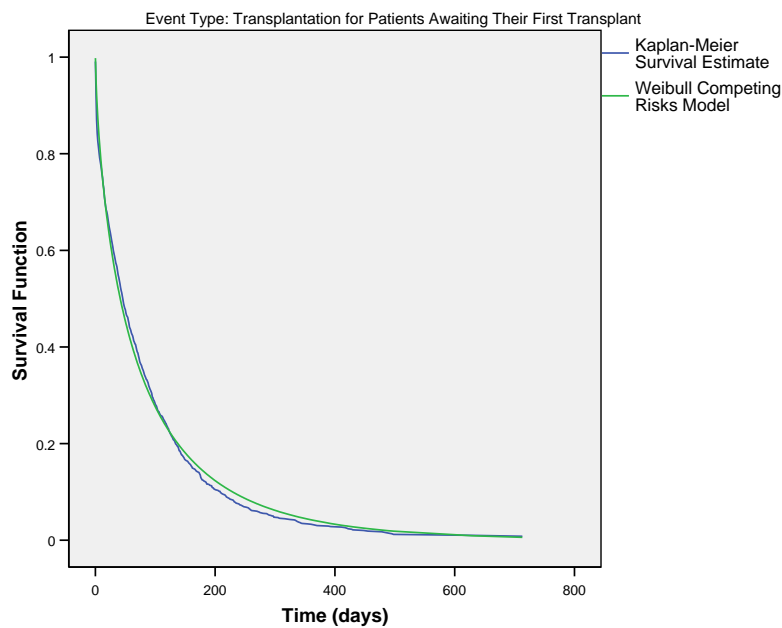


Figure J.22 Plot of the Kaplan-Meier estimate for survival and the estimated Weibull competing risks mode capturing the Transplantation outcome from the WL, for patients awaiting their first transplant.

J.3 Models to Use

The model implemented in Hepatica is the competing risk model, as outlined in Section J.2.4.

Appendix K

Post Transplant Outcome Model Analysis and Development

This appendix reports the development of three parametric survival models which capture the outcomes to death/graft failure (DGF) and re-listing (RL) post-transplantation, censored at all other events.

K.1 Preliminary Analysis

This section summarises the main findings of the preliminary analysis (as outlined in Section 3.6.3 part [A]). Only the graphs and tests which help to decide which parametric models are appropriate are presented here, however the analysis was performed for all covariates.

K.1.1 Identifying Significant Differences in Patient Survival by Covariate Levels

Below is a summary of the Log Rank and Wilcoxon tests (pooled over strata) which were used to identify the covariates by which the survival curves were significantly different. The tests were based on identifying the outcome death/graft failure or re-listing and censoring at all other outcomes.

Table K.1 Tests to Identify Covariates which Lead to Significantly Different Survival Outcomes post transplantation.

Significance of Tests	Log Rank	Wilcoxon (Breslow)	Tarone-Ware
Donor-Patient ABO Match	<0.001	<0.001	<0.001
Cold ischaemic times	0.395	0.355	0.365
Donor age	0.043	0.033	0.037
Donor cause of death	0.553	0.575	0.582
First Transplant	<0.001	<0.001	<0.001
Completeness of liver used	0.049	0.018	0.027
Disease Group	<0.001	<0.001	<0.001
Patient age at transplant	0.117	0.084	0.092
Patient/Donor Rhesus match	0.410	0.626	0.530
MELD score	<0.001	<0.001	<0.001
Donor gender to patient gender	0.436	0.357	0.394
Donor weight – patient weight	0.010	0.040	0.060
Patient Body Mass Index	0.004	0.007	0.006
Urgency of transplant	<0.001	<0.001	<0.001
Patient gender	0.126	0.076	0.091

Initial analysis shows that the survival functions are significantly different over the following factors: donor-patient ABO match, donor age (greater than 65 years or not), first transplant or not, urgency of transplant, completeness of liver used in the transplant, primary liver disease at registration, MELD score, donor weight minus patient weight, and patient BMI. Pair-wise comparisons for levels within each covariate also gave similar conclusions but identified which levels were most different. Other factors which might lead to significantly different outcomes (from interpreting the results in Table K.1) include patient age at transplant and patient gender.

K.1.2 Should the event Death/Graft Failure be modelled separately to Re-Listing?

Analysis, including the creation of a logistic regression model implied that the patients who are re-listed do not have significantly different attributes to patients that experience death/graft failure. Analysis of the times to both events also implied no significant difference over the observation period.

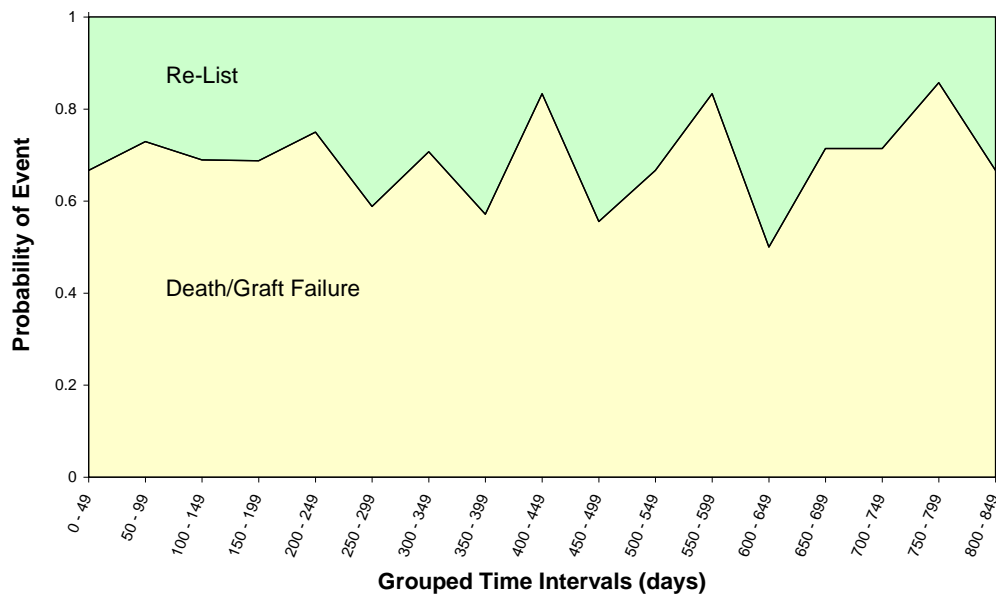


Figure K.1 The proportions observed to experience the events Death/Graft Failure and Re-Listing over Grouped Periods of Time Since Transplantation.

Figure K.1 shows that when considering the two events death/graft failure and re-listing through time, roughly 68% of events are death/graft failure and 32% are re-listings. The proportions remain roughly constant through time. This means that one model can be developed to capture the event DGFR (death/graft failure or re-listing) and that 68% of these events will be assigned as death/graft failure and the rest re-listing, at random.

K.1.3 Is a PH model appropriate?

Figure K.2 considers whether the Proportional Hazards (PH) assumption holds in modelling the survival distributions by donor and patient blood group match (comparing identical blood group matches with non identical blood group matches). The lines are reasonably parallel after the first few days, however, over the first few days the distance between the lines changes drastically, meaning that a proportional hazards model is probably not suitable in capturing the event death/graft failure or re-listing censored at all other events.

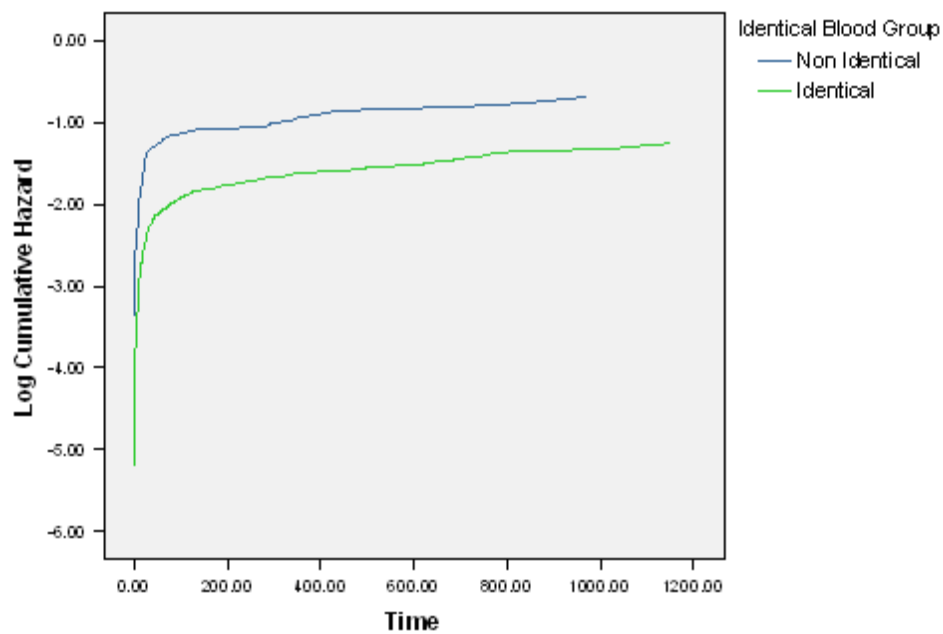


Figure K.2 Log-Cumulative Hazard Plot, by Identical Blood Group Match.

K.1.4 Is an AFT model appropriate?

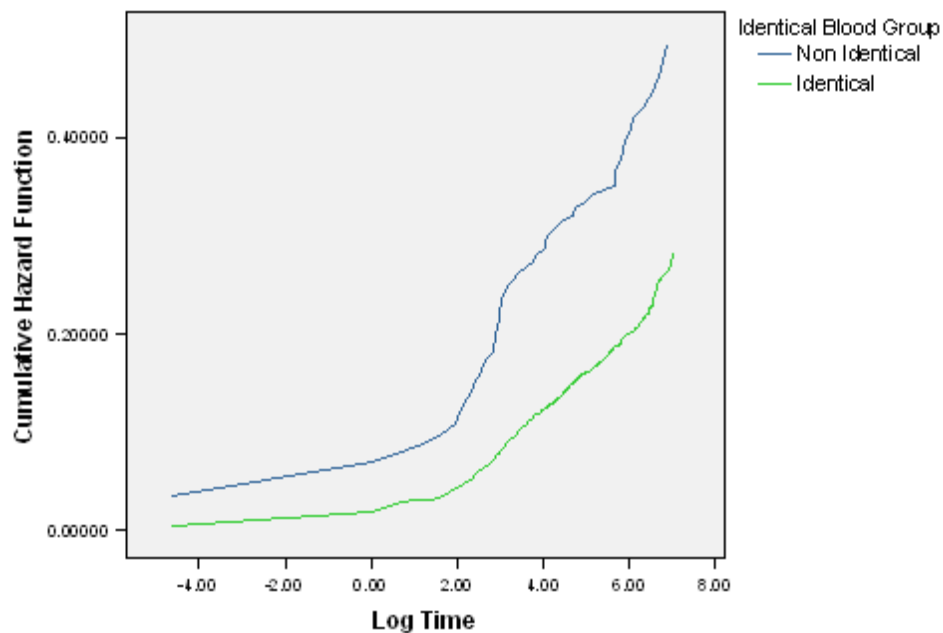


Figure K.3 Cumulative Hazard Plot, by Identical Blood Group Match.

Figure K.3 considers whether the accelerated failure time models are suitable in modelling the survival distributions by donor and patient blood group match (comparing identical blood group matches with non identical blood group

matches). The lines are reasonably parallel and straight which would suggest that an AFT model is suitable in capturing the event death/graft failure or re-listing censored at all other events.

Further plots indicated that any of the AFT survival models (Weibull, Log Logistic, or Lognormal) would be appropriate in capturing the post transplant outcomes. Therefore, all these models were developed and the best one chosen to use in the simulation.

K.1.5 Is a PH competing risks model appropriate?

Figure K.4 indicates that the PH competing risks model is not suitable for capturing the post transplant outcomes, since the log cumulative hazard lines cross.

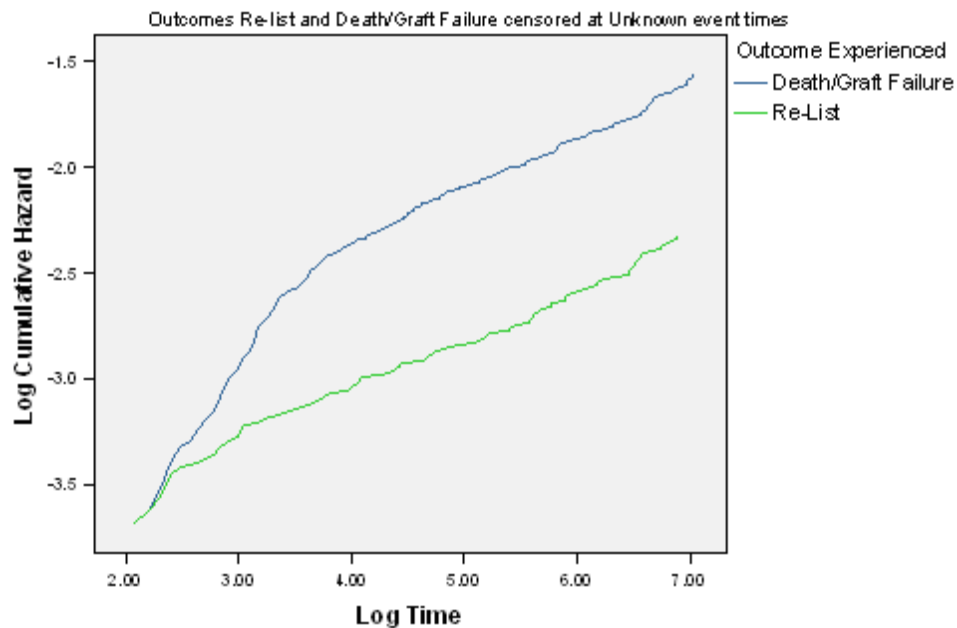


Figure K.4 Checking the Proportional Hazards Assumption of the Competing Risks Model for the Post Transplant Outcomes.

K.1.6 Is an AFT competing risks model appropriate?

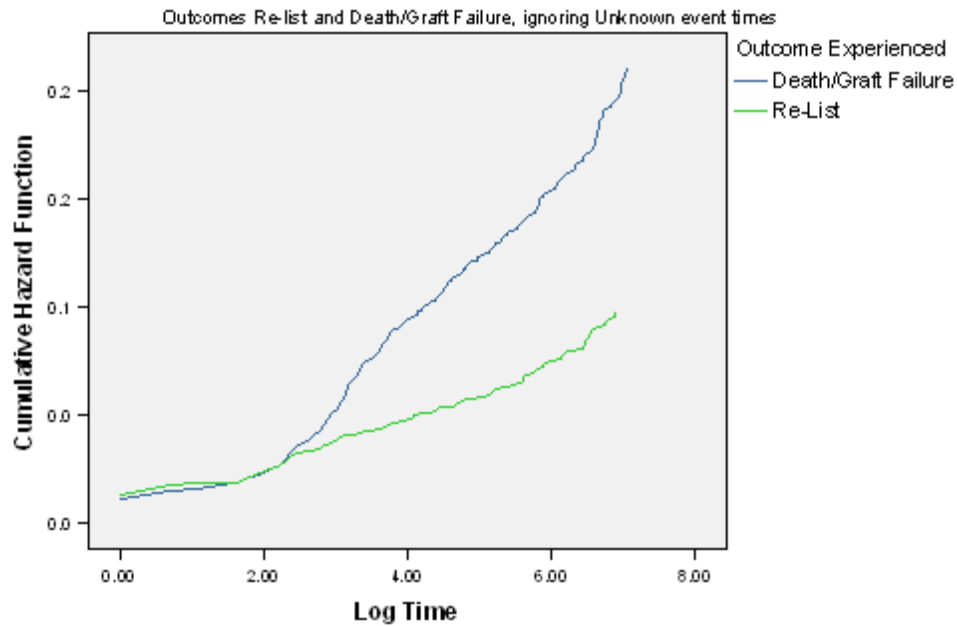


Figure K.5 Checking the Accelerated Failure Time Assumption of the Competing Risks Model for the Post Transplant Outcomes.

Figure K.5 indicates that the AFT competing risks model is not suitable for capturing the post transplant outcomes, since the cumulative hazard lines cross.

K.1.7 Summary

From section K.1.1 we can see that the attributes which significantly influence post transplant outcomes, are: donor-patient ABO match, donor age (greater than 65 years or not), first transplant or not, urgency of transplant, completeness of liver used in the transplant, primary liver disease at registration, MELD score, donor weight minus patient weight, and patient BMI.

From the analysis performed in section K.1.2-K.1.6 it was concluded that the models most appropriate for capturing the post transplant outcomes, are AFT survival models.

K.2 Parametric Model Development & Goodness of Fit

This section summarises the parametric models developed using the process as outlined in Section 3.6.3 part [B].

K.2.1 Weibull Survival Model

K.2.1.1 Model Development - Weibull Survival Model

Table K.2 The overall development process for the Weibull model (DGF/RL).

Stage	Enter/Exit	Variable(s)	Loglik(model)
a)	Enter	-Whole Liver -Split Liver -First Transplant -Donor Gender -Donor Age Group (≥ 65 years) -Donor Cause of Death Due to Trauma -Donor Cause of Death Due to Infection -Donor Weight minus Patient Weight -Female Donor to Female Patient -Patient Age -Transplant Urgency -Patient Underweight -Patient Obese -Other Cirrhotic Disease Group -Other Diagnosed Disease Group -Super Urgent or Acute Disease Group -Alcoholic Liver Disease -Identical Blood Groups -Compatible Blood Groups -MELD Group 2 -MELD Group 3 -MELD Group 4	-2933
b)	Exit	-Split Liver -Transplant urgency -MELD Group 2	-2933.2
	Exit	-Patient Obese	-2933.4
	Exit	-Donor Cause of Death Due to Trauma	-2933.7
	Exit	-MELD Group 4	-2934
	Exit	-Donor Gender	-2934.8
	Exit	-First Transplant	-2935.8
c)	-	-Whole Liver -Donor Age Group (≥ 65 years) -Donor Cause of Death Due to Infection -Donor Weight minus Patient Weight -Patient Age -Other Cirrhotic Disease Group -Other Diagnosed Disease Group -Super Urgent or Acute Disease Group -Alcoholic Liver Disease	-2935.8

K.2.1.2 Final Model - Weibull Survival Model

Table K.3 Final Weibull Model for Capturing the Event DGF/RL.

Attributes	Coefficient	Standard Error	Z	p-value
(Intercept)	4.6041	2.20341	2.09	3.67x10-02
Whole Liver	1.6491	0.58913	2.8	5.12x10-03
Donor Age Group (≥ 65 years)	-1.0423	0.4278	-2.44	1.48x10-02
Donor Cause of Death Due to Infection	-1.9357	0.96616	-2	4.51x10-02
Donor Weight minus Patient Weight	-0.0258	0.00959	-2.69	7.08x10-03
Patient Age	-0.0354	0.01267	-2.79	5.27x10-03
Other Cirrhotic Disease Group	0.8842	0.46082	1.92	5.50x10-02
Other Diagnosed Disease Group	-1.3874	0.60211	-2.3	2.12x10-02
Super Urgent or Acute Disease Group	-2.2331	0.41046	-5.44	5.31x10-08
Alcoholic Liver Disease	1.3008	0.53598	2.43	1.52x10-02
Identical Blood Groups	6.6536	2.0359	3.27	1.08x10-03
Compatible Blood Groups	5.6068	2.05649	2.73	6.40x10-03
MELD Group 3	-0.9883	0.36178	-2.73	6.30x10-03
Log(scale)	1.0419	0.04769	21.84	8.73x10-106

Loglik(model)= -2935.8 Loglik(intercept only)= -2989.9

Chisq= 108.26 on 12 degrees of freedom, p= 0

K.2.1.3 Goodness of Fit - Weibull Survival Model

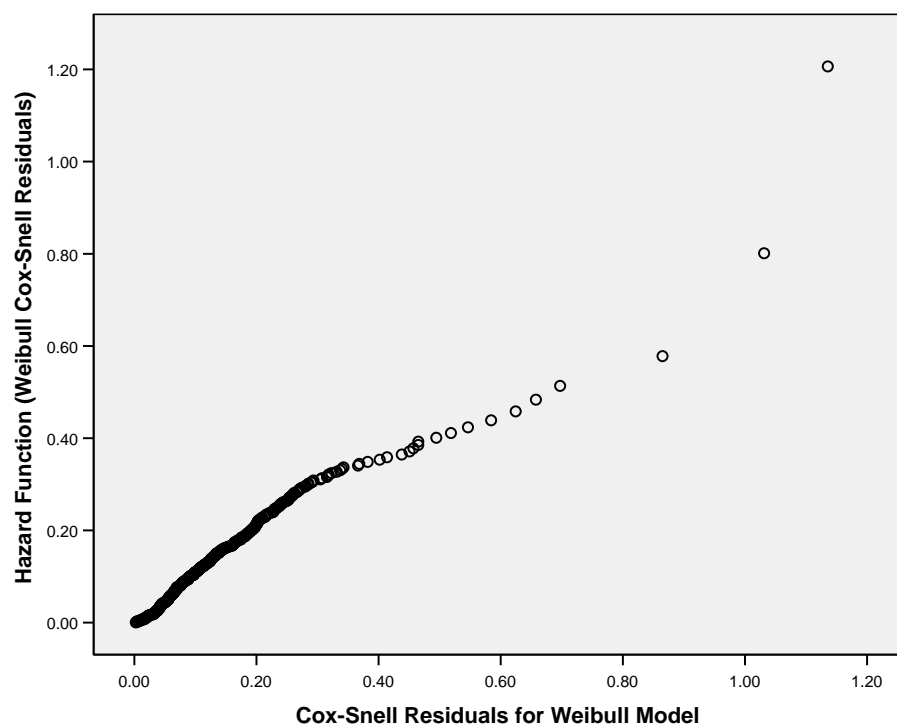


Figure K.6 Cumulative hazard plot of the Cox-Snell residuals generated from the Weibull model developed for the outcome DGF/RL.

Table K.4 The result (model summary and coefficients) of performing linear regression (with no covariates) on the graph depicted in Figure K.6.

Model	Unstandardised Coefficients		Standardised Coefficients	t	Significance
	B	Std. Error	Beta		
(Constant)	0.016	0.002		8.601	<0.001
Cox Snell Residual for Lognormal model	0.888	0.010	0.977	92.834	<0.001

$R^2 = 0.977$

K.2.2 Log-Logistic Survival Model

K.2.2.1 Model Development - Log-Logistic Survival Model

Table K.5 The overall development process for the Log-Logistic model (DGF/RL).

Stage	Enter/Exit	Variable(s)	Loglik(model)
a)	Enter	-Whole Liver -Split Liver -First Transplant -Donor Age Group (≥ 65 years) -Donor Cause of Death Due to Infection -Donor Weight minus Patient Weight -Female Donor to Female Patient -Patient Age -Transplant Urgency -Patient Underweight -Patient Normal Weight -Patient Obese -Other Cirrhotic Disease Group -Other Diagnosed Disease Group -Super Urgent or Acute Disease Group -Alcoholic Liver Disease -Identical Blood Groups -Compatible Blood Groups -MELD Group 1 -MELD Group 2 -MELD Group 4	-2927.5
b)	Exit	-Transplant Urgency -Patient Underweight -Patient Normal Weight	-2927.5
	Exit	-Split Liver	-2927.6
	Exit	-Female Donor to Female Patient	-2927.7
	Exit	-Patient Obese	-2928
	Exit	-MELD Group 4	-2928.7
	Exit	-MELD Group 1	-2929.8
	Exit	-Compatible Blood Groups	-2930.9
c)	Enter	-Whole Liver -First Transplant -Donor Age Group (≥ 65 years) -Donor Cause of Death Due to Infection -Donor Weight minus Patient Weight -Patient Age -Other Cirrhotic Disease Group -Other Diagnosed Disease Group -Super Urgent or Acute Disease Group -Alcoholic Liver Disease	-2930.9

K.2.2.2 Final Model - Log-Logistic Survival Model

Table K.6 Final Log-Logistic Model for Capturing the Event DGF/RL.

Attributes	Coefficient	Standard Error	Z	p-value
(Intercept)	9.1516	1.0062	9.1	9.42x10-20
Whole Liver	1.8506	0.6378	2.9	3.71x10-03
Donor Age Group (≥ 65 years)	-1.047	0.4481	-2.34	1.95x10-02
Donor Cause of Death Due to Infection	-2.4763	1.1041	-2.24	2.49x10-02
Donor Weight minus Patient Weight	-0.0279	0.0101	-2.77	5.61x10-03
Patient Age	-0.0373	0.0134	-2.78	5.39x10-03
Other Cirrhotic Disease Group	0.8896	0.4635	1.92	5.49x10-02
Other Diagnosed Disease Group	-1.5045	0.6336	-2.37	1.76x10-02
Super Urgent or Acute Disease Group	-2.3895	0.4333	-5.51	3.50x10-08
Alcoholic Liver Disease	1.3394	0.5305	2.52	1.16x10-02
Identical Blood Groups	1.2883	0.4853	2.65	7.94x10-03
MELD Group 3	-1.0072	0.3856	-2.61	9.00x10-03
Log(scale)	0.944	0.0464	20.34	6.02x10-92

Loglik(model)= -2930.6 Loglik(intercept only)= -2985.6

Chisq= 110.11 on 11 degrees of freedom, p= 0

K.2.2.3 Goodness of Fit - Log-Logistic Survival Model

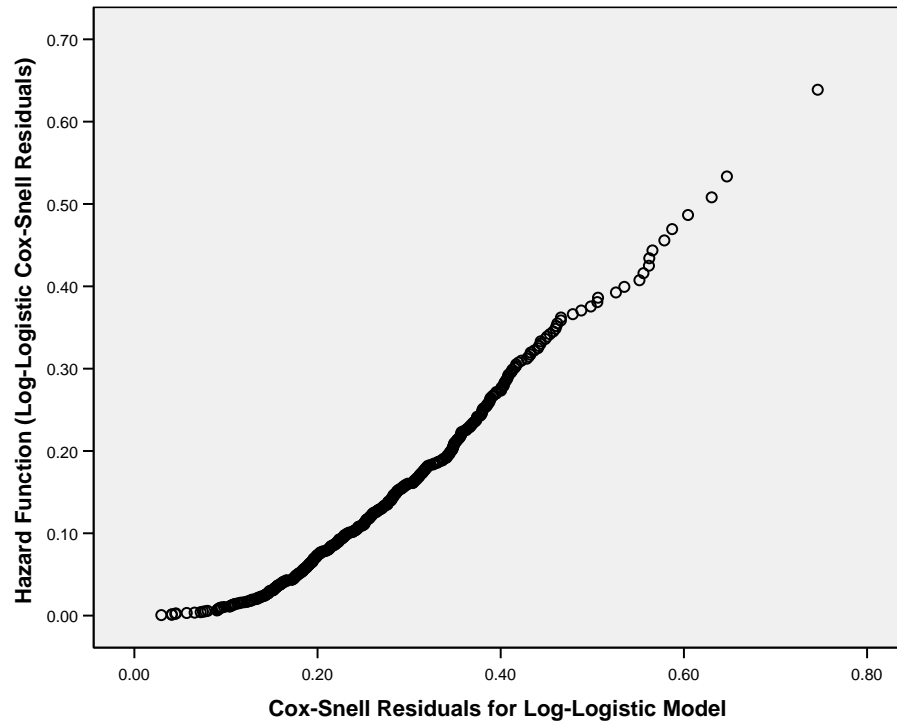


Figure K.7 Cumulative hazard plot of the Cox-Snell residuals generated from the Log-Logistic model developed for the outcome DGF/RL.

Table K.7 The result (model summary and coefficients) of performing linear regression (with no covariates) on the graph depicted in Figure K.7.

Model	Unstandardised Coefficients		Standardised Coefficients	t	Significance
	B	Std. Error	Beta		
(Constant)	-0.111	0.002		-55.129	<0.001
Cox Snell Residual for Log-Logistic model	0.943	0.007	0.989	136.468	<0.001

$R^2 = 0.978$

K.2.3 Lognormal Survival Model

K.2.3.1 Model Development - Lognormal Survival Model

Table K.8 The overall development process for the Lognormal model (DGF/RL).

Stage	Enter/Exit	Variable(s)	Loglik(model)
a)	Enter	-Whole Liver -Split Liver -First Transplant -Donor Cause of Death Due to Infection -Donor Weight minus Patient Weight -Patient Age -Transplant Urgency -Patient Normal Weight -Patient Obese -Other Cirrhotic Disease Group -Cholestatic Liver Disease -Other Diagnosed Disease Group -Super Urgent or Acute Disease Group -Alcoholic Liver Disease -Identical Blood Groups -Compatible Blood Groups -MELD Group 2 -MELD Group 3 -MELD Group 4	-2922.4
b)	Exit	-Split Liver -Patient Normal Weight -MELD Group 2	-2922.5
	Exit	-Transplant urgency -Patient Obese	-2922.7
	Exit	-First Transplant -MELD Group 4	-2923.4
	Exit	-Cholestatic Liver Disease	-2923.8
	Exit	-Compatible Blood Groups	-2924.8
	-	-Whole Liver -Donor Cause of Death Due to Infection -Donor Weight minus Patient Weight -Patient Age -Other Cirrhotic Disease Group -Other Diagnosed Disease Group -Super Urgent or Acute Disease Group -Alcoholic Liver Disease -Identical Blood Groups -MELD Group 3	-2924.8
c)	Enter	-Donor Age Group (≥ 65 years) -Donor Death Due to Intracranial Injuries	-2921.3
b)	Exit	-Donor Death Due to Intracranial Injuries	-2922.5

K.2.3.2 Final Model - Lognormal Survival Model

Table K.9 Final Lognormal Model for Capturing the Event DGF/RL.

Attributes	Coefficient	Standard Error	Z	p-value
(Intercept)	9.3227	1.0702	8.71	3.01x10-18
Whole Liver	1.925	0.6785	2.84	4.55x10-03
Donor Cause of Death Due to Infection	-2.6866	1.1644	-2.31	2.10x10-02
Donor Weight minus Patient Weight	-0.0304	0.0105	-2.89	3.86x10-03
Patient Age	-0.0349	0.0141	-2.48	1.32x10-02
Other Cirrhotic Disease Group	0.8948	0.4706	1.9	5.73x10-02
Other Diagnosed Disease Group	-1.4859	0.6766	-2.2	2.81x10-02
Super Urgent or Acute Disease Group	-2.3982	0.4613	-5.2	2.01x10-07
Alcoholic Liver Disease	1.3821	0.5322	2.6	9.41x10-03
Identical Blood Groups	1.3937	0.5313	2.62	8.71x10-03
MELD Group 3	-0.9671	0.4115	-2.35	1.88x10-02
Donor Age Group (≥ 65 years)	-1.0273	0.4755	-2.16	3.08x10-02
Log(scale)	1.579	0.0422	37.41	3.13x10-306

Loglik(model)= -2922.5 Loglik(intercept only)= -2977.1

Chisq= 109.32 on 11 degrees of freedom, p= 0

K.2.3.3 Goodness of Fit - Lognormal Survival Model

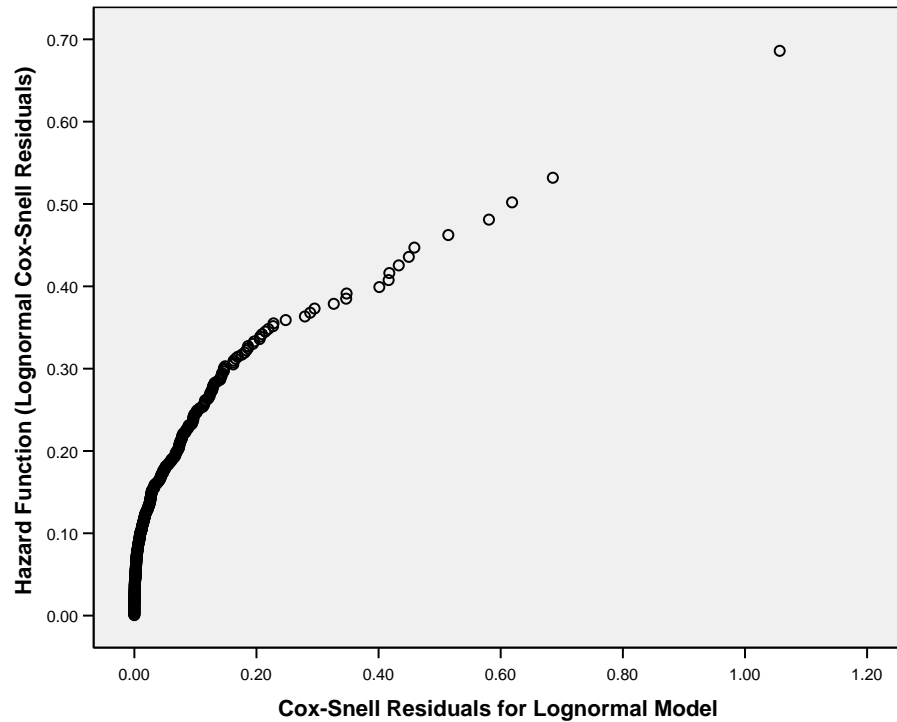


Figure K.8 Cumulative hazard plot of the Cox-Snell residuals generated from the Lognormal model developed for the outcome DGF/RL.

Table K.10 The result (model summary and coefficients) of performing linear regression (with no covariates) on the graph depicted in Figure K.10.

Model	Unstandardised Coefficients		Standardised Coefficients	t	Significance
	B	Std. Error	Beta		
(Constant)	0.091	0.003		30.827	<0.001
Cox Snell Residual for Lognormal model	0.898	0.025	0.873	36.564	<0.001

$R^2 = 0.762$

K.3 Model to Use

Figure K.9 compares the Kaplan-Meier Estimate with the parametric models fitted for the outcome death/graft failure or re-listing post transplant, censored at all other times. All the models fit well, and the log-logistic model was chosen

for use in Hepatica, as it returned the best results in the goodness of fit analysis (see Sections K.2.1.3, K.2.2.3, and K.2.3.3).

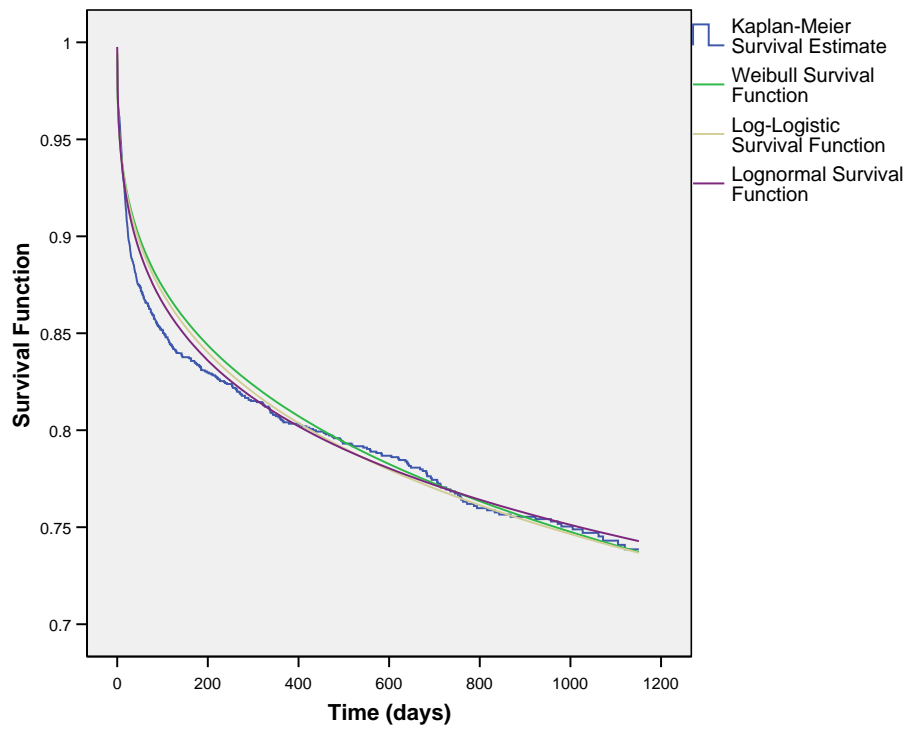


Figure K.9 Fitted Survival Models to the Post Transplant Outcomes and the Kaplan-Meier Survival Estimate.

Appendix L

Assigning Patient and Donor Attributes

L.1 Attributes to Assign

As explained previously (Section 3.6.1) the attributes that need to be assigned to patients and donors arriving into the system are those which play a significant role in patient progression through the system (i.e., those that determine pre- and post-transplant survival, and those that determine who is chosen for transplantation) and in patient and donor arrivals.

From the analysis in Sections 4.3-4.5 and the allocation rules as described in Section 3.3.4, the list of attributes which require assigning, are:

(1) for patients:

- a. the type of disease (only those groups significant in patient progression and survival);
- b. the urgency of the transplant required by the patient;
- c. age;
- d. first transplant or not;
- e. centre;
- f. gender;
- g. MELD group;
- h. weight;
- i. blood group.

(2) for donors:

- a. if the donated liver is a whole liver or a reduced/split liver;
- b. cause of death;
- c. weight;
- d. age;
- e. blood group;

f. centre.

L.2 Dependencies between Attributes

Before assigning attributes to the patients and donors within Hepatica, tests were performed to check if all the attributes could be assigned at random, or if there were any dependencies which needed to be taken into account.

L.2.1 Statistical Tests

Where the two attributes being compared both had a small number of values/factors, a contingency table was set up and the Chi-squared statistic evaluated to identify dependencies between the two attributes.

Where either one of the attributes was continuous or the other attribute a factor, then a test was performed to identify if the averages were significantly different (ANOVA techniques).

Where both attributes were continuous then a test to determine the correlation between the two variables was performed.

L.2.2 Data Sets Used

As we are assigning patient attributes as patients join the waiting list, we need to check the dependencies between variables for those that have joined the WL (as given by UK Transplant). This will avoid incorporating any bias as a result of the current allocation policy that is in. The donor attributes were tested using the donor data provided by UK Transplant. Dependencies between donor and patient attributes were not considered, as again these dependencies will arise from the allocation policy which is in place.

L.2.3 Missing Values

Cases with missing attributes were omitted for the tests which considered the attributes.

L.2.4 Tests to Determine the Dependencies between Patient

The chi-squared tests (Table L.1) confirmed dependencies between the patient attributes: (1) Disease group and Transplant urgency, (2) Disease group and First transplant, (3), Disease group and Transplant centre, (4) Disease group and gender, (5) Transplant urgency and First transplant, (6) Transplant centre and Transplant urgency, (7) Transplant urgency and gender, (8) Transplant urgency and MELD group, (9) First transplant and MELD group, and (10) Transplant centre and Blood group.

Table L.1 Results of Chi-Squared Tests for Patient Attributes.

Patient Attributes	Number of valid cases	Degrees of Freedom	Pearson Chi Square Value	Significance (2-sided)
disease group * urgency	2453	7	1424.733	<0.001
disease group * first transplant or not	2453	7	347.980	<0.001
disease group * centre	2453	42	203.875	<0.001
disease group * gender	2453	7	536.002	<0.001
disease group * meld	1948	7	8.801	0.267
disease group * blood group	2453	21	22.784	0.356
urgency * first transplant or not	2453	1	43.979	<0.001
urgency * centre	2453	6	22.572	0.001
urgency * gender	2453	1	50.127	<0.001
urgency * meld	1948	1	4.997	0.025
urgency * blood group	2453	3	2.240	0.524
first transplant or not * centre	2453	6	11.339	0.078
first transplant or not * gender	2453	1	1.090	0.297
first transplant or not * meld	1948	1	11.047	0.001
first transplant or not * blood group	2453	3	3.952	0.267
centre * gender	2453	6	6.304	0.390
centre * meld	1948	6	9.153	0.165
centre * blood group	2453	18	29.137	0.047
gender * meld	1948	1	0.928	0.335
gender * blood group	2453	3	0.437	0.932
meld * blood group	1948	3	1.388	0.708

The ANOVA tests (Table L.2) confirmed dependencies between the patient attributes weight and gender.

Table L.2 Results of ANOVA Tests for Patient Attributes.

Patient Attributes	Eta	Eta Squared
age * disease group	0.423	0.179
age * urgency	0.372	0.139
age * first transplant or not	0.109	0.012
age * centre	0.082	0.007
age * gender	0.077	0.006
age * meld	0.011	<0.001
age * blood group	0.061	0.004
weight * disease group	0.283	0.080
weight * urgency	0.061	0.004
weight * first transplant or not	0.110	0.012
weight * centre	0.055	0.003
weight * gender	0.412	0.170
weight * meld	0.027	0.001
weight * blood group	0.038	0.001

The correlation tests (Table L.3) confirmed dependencies between the patient attributes age and weight.

Table L.3 Results of Correlation Tests for Patient Attributes.

Patient Attributes	Number (valid cases)	Pearson	Significance (2-tailed)
age * weight	2372	0.139	<0.001

L.2.5 Tests to Determine the Dependencies between Donor Attributes

The chi-squared tests (Table L.4) confirmed dependencies between the donor attributes: (1) Whole liver and Cause of death, (2) Whole liver and Transplant centre, (3) Age and Whole liver, and (4) Age and Cause of death.

Table L.4 Results of Chi-Squared Tests for Donor Attributes.

Donor Attributes	Number of valid cases	Degrees of Freedom	Pearson Chi Square Value	Significance (2-sided)
whole * cause of death	2082	1	5.050	0.025
whole * blood group	2082	3	5.772	0.123
whole * centre	2082	6	35.674	<0.001
cause of death * blood group	2082	3	3.516	0.319
cause of death * centre	2082	6	5.566	0.474
blood group * centre	2082	18	16.662	0.546
age * whole	2082	1	15.194	<0.001
age * cause of death	2082	1	4.497	0.034
age * blood group	2082	3	5.693	0.128
age * centre	2082	6	7.474	0.279

The ANOVA tests (Table L.5) were not significant for any of the combination of donor attributes tested.

Table L.5 Results of ANOVA Tests for Donor Attributes.

Donor Attributes	Eta	Eta Squared
weight * whole	0.031	0.001
weight * donor cause of death	0.004	<0.001
weight * donor blood group	0.032	0.001
weight * centre	0.061	0.004
weight * age	0.012	<0.001

L.3 Summary of How the Attributes will be Assigned

As detailed in Section L.2 several dependencies were found, these are summarised in Table L.6 and are captured within Hepatica.

Table L.6 Dependencies Captured in Hepatica.

	Dependencies Between
Patient Characteristics	Disease group and Transplant urgency Disease group and First transplant Disease group and Transplant centre Disease group and Patient gender Transplant urgency and First transplant Transplant centre and Transplant urgency Transplant urgency and Patient gender Transplant urgency and MELD group First transplant and MELD group Transplant centre and Blood group Patient weight and Patient gender Patient age and Patient weight
Donor Characteristics	Whole liver and Donor cause of death Whole liver and Transplant centre Donor age and Whole liver Donor age and Donor cause of death

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